EVALUATION OF CARDIAC, HEMODYNAMIC, NEUROHUMORAL AND SKELETAL MUSCLE METABOLIC RESPONSES DURING AN ACUTE BOUT OF EXERCISE AND FOLLOWING EXERCISE TRAINING IN PATIENTS WITH HEART FAILURE

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Abstract of Dissertation Presented to the Graduate School of the University of Florida in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

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Heart failure is a syndrome in which a reduction in cardiac function results in a series of compensatory adaptations. Although, these adaptations initially develop in an attempt to normalize cardiocirculatory function, they exact a price and contribute to the significant morbidity and mortality associated with this disease. The present research was aimed at identifying factors that contributed to the clinical severity of heart failure and determined whether 16 weeks of exercise training would represent a beneficial treatment strategy. The acute response to exercise was evaluated in 34 patients with heart failure, 60±6 (mean±sd) years and compared to 8 healthy controls (63±6 years). Exercise capacity was markedly depressed in the patients (VO_{2peak} = 11.86±3.52 ml.kg^{-1}.min^{-1}) compared to controls (VO_{2peak} = 30.57±2.72 ml.kg^{-1}.min^{-1}). Two factors thought to contribute to the exercise intolerance included (1) a narrowing of hemodynamic and neurohumoral reserve capacity, and (2) impaired skeletal muscle energetics. Chronotropic reserve during a

symptom-limited exercise test was significantly less in heart failure compared to controls (54 ± 8 versus 82 ± 9 beats.min^{-1}). Stroke volume increased during low level exercise, but was followed by a decline at higher intensities resulting in a blunted cardiac output in the patients. Furthermore, resting neurohormones were elevated in the patients. Patients demonstrated a greater rise in the inorganic phosphate to phosphocreatine ratio (Pi/PCr) and intramuscular diprotonated inorganic phosphate ($H_2PO_4^-$) during, as well as prolonged phosphocreatine resynthesis following exercise. These data indicated a greater reliance on glycolytic pathways and impaired oxidative rephosphorylation.

The response to 16 weeks of exercise training (TR) was evaluated in 14 heart failure patients (61 ± 7 years) and compared to 14 patients (62 ± 8 years) who did not train (NTR). Exercise capacity and tolerance increased 24% and 31% in TR, with no change in NTR. Following TR, there was evidence of a wider hemodynamic reserve capacity suggesting an improved cardiopulmonary system. The TR group demonstrated a 26% to 32% reduction in pre-exercise angiotensin II, aldosterone, arginine vasopressin, and atrial natriuretic peptide, with no changes in NTR. Furthermore, TR resulted in improved skeletal muscle energetics, as evidenced by a 19% reduction in Pi/PCr, a 30% decline in $H_2PO_4^-$ during low and high intensity work, respectively, as well as a 26% to 37% improvement in recovery kinetics. Finally, the TR group patients demonstrated an improved perception of quality of life. These findings indicated that TR presents a profound stimulus in reversing the compensatory adaptations associated with heart failure and results in a significant increase in exercise tolerance and capacity.

CHAPTER 1
INTRODUCTION

Heart failure is defined as "the pathophysiological state in which an abnormality of cardiac function is responsible for failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues and/or to be able to do so only from an elevated filling pressure" (Braunwald, 1988, p.393). This definition implies that there is an alteration in the normal physiological pumping capacity of the heart. This alteration is principally due to three distinct etiologies (Sokolow & McIlroy, 1990) (1) intrinsic myocardial disease including coronary heart disease, cardiomyopathy, and infiltrative disease; (2) excess work load due to increased resistance to ejection (pressure load) secondary to hypertension and hypertrophic cardiomyopathy or increased stroke volume (volume load) secondary to aortic and/or valvular insufficiency; (3) iatrogenic myocardial damage from drugs (doxorubicin and disopyramide) or radiation therapy for mediastinal tumors or Hodgkin's disease.

The most recent Heart and Stroke Facts published by the American Heart Association (1996) present the statistics associated with heart failure. About 4.7 million Americans are thought to have some degree of heart failure. Each year 400,000 new cases of heart failure are diagnosed. In 1992, 36,387 Americans died from heart failure. In an additional 250,000 deaths complications associated with heart failure were a

significant contributing factor. At particular risk for the development of heart failure are elderly individuals. In fact, heart failure is the most common hospital discharge diagnosis in patients over 65 years. In addition to the cost of human life, heart failure poses an enormous financial burden on American society (Kannel et al., 1988). In 1990, heart failure accounted for annual expenditures exceeding $4.5 billion (Blumenfeld & Laragh, 1994). It is expected that this cost to society will only rise in the future, as it is estimated that by the year 2030, the number of persons over 65 years of age will exceed those under 65. This will undoubtedly result in a significant increase in the number of people with heart failure (Ghali et al., 1990).

The treatment of heart failure is aimed at correcting the underlying cause and/or controlling the heart failure state (Smith et al., 1988). The management of the heart failure patient, generally, includes a combination of pharmacological compounds aimed to relieve clinical symptoms and prolong life (Parmley, 1989; Rahimtoola, 1989; Remme, 1994). Numerous pharmacological agents are available which help improve central hemodynamics by reducing cardiac afterload or enhancing myocardial contractility. Additional pharmacological agents are used to reduce excessive fluid retention. Following initiation of such therapy mortality is reduced, and many patients experience resolution of their symptoms at rest (Cohn et al., 1986; Feldman et al., 1993; Lenfant, 1994; Pepine, 1996; Remme, 1994; SOLVD Investigators, 1991, 1993; Swedberg, 1992). However, most patients continue to experience activity-related symptoms, including shortness of breath, muscle fatigue, and weakness. As a result patients with heart failure often complain of chronic fatigue and are unable to perform many of their normal

activities of daily living. Thus, despite traditional pharmacologic treatment, the clinical phase of heart failure includes a marked decline in functional state, as defined by exercise tolerance and capacity with a subsequent decrease in quality of life.

Intuitively, one would hypothesize that the clinical severity of heart failure is directly related to the degree of cardiac dysfunction. Yet, most clinical measures of cardiac function (e.g. cardiothoracic ratio; left ventricular ejection fraction (LVEF)) correlate poorly with the clinical severity of heart failure, as defined by exercise tolerance or capacity (Benge et al., 1981; Franciosa et al., 1980; McKirnan et al., 1984). This discordance has led to the identification of multiple compensatory mechanisms with short- to long-time constants, which may contribute to the marked exercise intolerance in heart failure (Drexler et al., 1991, 1992; Kubo et al., 1991; Lipkin et al.,1988; Mancini et al., 1989, 1992; Massie et al., 1988; Sullivan et al., 1990; Zelis et al., 1991). These compensatory mechanisms include: (1) "hyper"-activation of neurohumoral factors, e.g. increased catecholamines and fluid-regulatory hormones (Drexler et al., 1991; Zelis et al., 1991) and a decrease in endothelium-mediated dilators (Kubo et al., 1991), (2) alterations in skeletal muscle blood flow, metabolism and function (Drexler et al., 1992; Lipkin et al., 1988; Mancini et al., 1989, 1992; Massie et al., 1988; Sullivan et al., 1990), and (3) structural vascular and skeletal muscle changes (Drexler et al., 1987, 1988, 1992; Zelis et al., 1968, 1970, 1975, 1982, 1991).

Several clinical trials have established the independent prognostic importance of many of the above mentioned peripheral compensatory adaptations to heart failure. For example, data from the Department of Veterans Affairs Cooperative Vasodilator-Heart

Failure Trials (V-HeFT I and II) identified plasma norepinephrine as a strong independent predictor of mortality (Cohn et al. 1984, 1992). In the multicenter Scandinavian trial CONSENSUS patients with high baseline levels of Angiotensin II and Aldosterone had significantly greater rates of mortality (Swedberg et al. 1990, 1992). These data suggested that mortality in heart failure is linked to the activation of the sympathetic nervous system and/or the renin-angiotensin-aldosterone system. A similar correlation with mortality has been reported for other fluid regulatory hormones such as vasopressin (Benedict et al, 1993; Packer et al. 1988) and atrial natriuretic peptide (Davis et al., 1992; Gottlieb et al. 1989). In addition, exercise capacity, defined by VO_{2peak}, has also been identified as a considerable determinant of prognosis in heart failure (Cohen-Solal et al., 1994; Cohn & Rector, 1988; Mancini et al., 1991; Parameshwar et al., 1992; Roul et al., 1994; Szlachcic et al., 1985). This should come as no surprise since the major determinants of exercise capacity are cardiac output and peripheral oxygen extraction, both of which are affected in heart failure.

Although, the purpose of the compensatory adaptations in heart failure is thought to be an attempt to maintain a cardiac output and arterial pressure that adequately perfuses the brain and the heart, it is the magnitude of these compensatory adaptations that eventually sows the seed for a series of maladaptive processes which lead to a decompensated state or even end-stage heart failure (Zelis, 1991). Yet, to date, it is not clear to what degree the compensatory adaptations in heart failure are inherent to the disease or to other contributing factors such as physical deconditioning and/or malnutrition. Zelis, et al. (1982) hypothesized that the peripheral alterations in heart

failure are in part protective as they prevent blood pressure from decreasing when the failing heart cannot adequately increase cardiac output. Others suggest that the peripheral alterations in heart failure in part mimic the deconditioning process seen with prolonged physical inactivity (Adamopoulos & Coats, 1991; Minotti et al., 1990; Stratton et al., 1994; Sullivan et al., 1988). Thus, it is presently not clear to what degree the exercise intolerance in heart failure is inherent to the disease itself, level of inactivity, or one or more unidentified contributing factors.

Until the late 1980s physical activity for heart failure patients was discouraged and many patients were told to refrain from physical exertion (Burch & De Pasquale, 1966; Dubach & Froelicher, 1989; Froelicher, 1987; Wenger, 1978). This conservative approach was due to a concern for a greater risk for cardiovascular complications during exercise. Arguably, this conservative approach has contributed to the considerable morbidity in heart failure patients. More recent reports indicate that heart failure patients can safely participate and benefit from exercise training programs (Arvan, 1988; Baigrie et al., 1992; Coats et al., 1990, 1992; Conn et al., 1982; ; Jette et al., 1991; Jugdutt et al., 1988; Lee et al., 1979; Sullivan et al., 1988). From these reports it is clear that the heart failure patient can increase exercise capacity and tolerance following exercise training. As a result exercise training is slowly emerging as a beneficial adjunct to the management of patients with heart failure. Even though the above-mentioned reports are promising, few studies have been of sufficient length to determine the effect of exercise training on the time-dependent compensatory adaptations and whether exercise training has a long-term impact on morbidity and mortality in heart failure. Furthermore, it is surprising that

only three studies have used a randomized design to determine the role of exercise training in the management of the heart failure patient. Thus, there is a need to confirm the reports currently available and to determine the feasibility, clinical benefit and safety of exercise training in a long-term progressive, randomized trial.

In summary, despite advances in the management of patients with heart failure, most patients continue to experience activity-related symptoms and are often unable to perform many of the normal activities of daily living. There appears to be strong evidence that the exercise intolerance in heart failure is at least in part linked to the activity of peripheral compensatory mechanisms, including neurohumoral, vascular and skeletal muscle factors. Recent evidence shows that exercise training reverses some of the peripheral abnormalities present in heart failure. Thus, the use of exercise training may be an important adjunct therapeutic modality for patients with heart failure.

Justification for Research

A decline in exercise capacity has been shown to be a most powerful predictor of mortality in heart failure patients (Cohen-Solal et al., 1994; Cohn et al., 1993; Mancini et al., 1991; Parameshwar et al., 1992; Roul et al., 1994; Szlachcic et al., 1985). Paradoxically the degree of left ventricular dysfunction does not correlate with the functional state (exercise capacity) of patients with heart failure (Benge et al., 1980; Franciosa et al., 1979, 1980; McKirnan et al., 1984). This has resulted in the identification of multiple peripheral compensatory mechanisms with short- to long-term time constants that may limit exercise capacity in heart failure. Thus, heart failure is a syndrome in which a reduction in cardiac function results in a myriad of peripheral

adaptations, which subsequently contribute to a reduction in functional capacity and quality of life. Interestingly, it is not clear to what degree the compensatory adaptations in heart failure are inherent to the disease or to a process of deconditioning or other factors. Therefore, in order to increase the understanding of the symptoms associated with heart failure, further studies are needed to determine how and to what extent the compensatory adaptations to heart failure are changed during an acute bout of exercise. In addition, long-term studies are warranted to determine the effect of exercise training on central hemodynamics, neurohumoral activation, and skeletal muscle function. Ultimately, trials should be conducted to determine whether exercise training can impact the morbidity and mortality associated with heart failure.

Cardiac Responses to Acute and Chronic Exercise in Heart Failure

Heart failure is associated with either an increase in cardiac filling pressures, a decrease in cardiac output, or both, at rest and during exercise when compared to healthy age-matched controls. A reduction in cardiac output during exercise is an important factor limiting exercise tolerance in patients with heart failure (Sullivan et al. 1989).

Previous studies which have examined the cardiac response to an acute bout of exercise in patients with heart failure demonstrated characteristic responses to dynamic exercise. However, as functional class declines there is a progressive decrease in the cardiac output, stroke volume, blood pressure and heart rate reserve capacity (Hanson, 1994). Yet, few studies have assessed cardiac function during an upright activity, such as walking. Such information could potentially provide important clinical data, since most patients have to be able to walk to perform many daily activities.

There is no evidence of any change in LVEF after exercise training in the current heart failure trials. Resting cardiac output shows either no change (Sullivan et al., 1988) or a small increase (Coats et al., 1990). Peak exercise values for cardiac output increases and is generally achieved at a greater absolute workload (Coats et al., 1990). Exercise heart rates and rate pressure products at the same relative submaximal intensities are generally lower following training, possibly indicating a more efficient utilization of myocardial work and oxygen consumption (Coats et al., 1990).

The progressive narrowing of the hemodynamic reserve capacity in heart failure appears to be closely related to VO_{2peak} (Weber et al., 1982). Further studies are needed to determine whether exercise training can increase the hemodynamic reserve capacity in heart failure.

Neurohumoral Responses to Acute and Chronic Exercise in Heart Failure

Excessive neurohumoral activation appears to be a biochemical hallmark in many patients with heart failure and may reflect alterations in cardiovascular control mechanisms (Drexler, 1991; Hirsch et al., 1987; Kubo et al., 1983). However, it is not uncommon for patients recovering from an acute bout of heart failure to have a near normal neurohumoral profile (Dzau et al., 1981). Therefore, measurements of plasma hormones at rest may not be a sensitive marker of the clinical severity of heart failure. In contrast physical activity may unmask the underlying neurohumoral abnormalities.

Limited data are available regarding the effect of exercise training on neurohumoral activation in patients with heart failure. Coats et al. (1992) found evidence of a reduction in sympathetic tone, increase in vagal tone, and a reduction of

norepinephrine spillover at rest following an 8 week training regimen. These findings suggested that exercise training may help reverse the neurohumoral activation present in heart failure patients.

Thus, evaluation of the neuroendocrine responses during an acute exercise bout and following a period of exercise training may offer a more complete understanding of the activity of the compensatory mechanisms in heart failure. Such information could provide the clinician with an opportunity to determine a more optimal treatment strategy.

Skeletal Muscle Energetics during Acute and Chronic Exercise in Heart Failure

In recent years several investigators have focused on skeletal muscle as determinants of exercise limitation in patients with heart failure (Drexler et al., 1987, 1992; Dunnigan et al., 1984, 1987; Lipkin et al., 1988; Mancini et al., 1989, 1992; Massie et al., 1987, 1988; Marzo et al. 1993; Rajagopalan et al., 1988; Sullivan et al., 1990). The majority of these studies reported intrinsic skeletal muscle abnormalities that could contribute to the development of early lactic acidosis and fatigue during exercise in patients with heart failure. Interestingly, most studies have evaluated skeletal muscle metabolic responses during a ramp test, whereas relative few studies have compared the skeletal muscle metabolic responses between low- and high-intensity exercise. Although, a ramp test may provide the clinician with important information, a submaximal exercise bout may enhance the present understanding of the causes of fatigue during regular daily activities. Furthermore, a recent study reports that patients with heart failure have much slower recovery kinetics following a bout of exercise (Cohen-Solal et al., 1995). A slower recovery from physical activity may in part explain why patients with heart failure

often complain of symptoms of chronic fatigue. Certainly, studies aimed to further elucidate those factors that may help explain why patients with heart failure have such a limited exercise capacity and tolerance, as well as inability to recover from seemingly minor daily activities may be very important in optimizing treatments.

To date, there are only three studies which have examined the effect of an exercise training program on skeletal muscle metabolism and function in heart failure patients. The results of these studies were all promising as evidenced by an improved metabolic profile following exercise training, indicating that at least some of the skeletal muscle abnormalities are reversible. Unfortunately, the lengths of the three studies were all less than 8 weeks providing little information on the long-term impact of exercise training on the skeletal muscle compensatory adaptations to heart failure. Thus, additional studies are needed to further evaluate the skeletal muscle metabolic adaptations to exercise training in heart failure, and whether such adaptations relate to a change in functional capacity, as defined by exercise tolerance and capacity.

Exercise Training and Heart Failure

Traditionally, heart failure patients were told to remain sedentary. This conservative approach was a result of a concern for a greater risk for cardiovascular complications during exercise, and the belief that heart failure patients would not benefit from training (Burch & DePasquale, 1966,; Dubach & Froelicher, 1989; Wenger et al., 1978). A number of recent studies suggests that patients with left ventricular dysfunction can improve exercise capacity without adverse affects (Arvan, 1988; Baigrie et al., 1992; Coats et al., 1990, 1992; Conn et al., 1982; ; Jette et al., 1991; Jugdutt et al., 1988; Lee et

al., 1979; Sullivan et al., 1988). Despite evidence showing that exercise training results in improved exercise tolerance, the optimal frequency, duration, intensity, mode and progression of exercise to maximize the potential benefits of training are currently not well understood (Coats, 1993; McKelvie et al., 1995; Sullivan & Hawthorne, 1995). Therefore, research must be conducted to identify the optimal manner in which exercise may be prescribed for heart failure patients.

Exercise training in normal individuals leads to an increase in exercise capacity through both central and peripheral adaptations (Booth & Thomason, 1991; Clausen, 1976; Holloszy & Booth, 1976). It appears that in heart failure patients changes in exercise capacity are achieved primarily through peripheral alterations (Sullivan et al., 1988). Although the exact mechanism(s) involved in the peripheral adaptations is (are) not fully understood, exercise training may improve skeletal muscle blood flow (Sullivan et al., 1988), oxidative enzyme activity, and autonomic function (Coats et al., 1990). Analysis of skeletal muscle biopsies in heart failure patients indicated a reduced oxidative capacity and early onset of anaerobic metabolism (Drexler et al., 1988, 1992; Mancini et al., 1989). Exercise training has shown to increase the oxidative capacity of skeletal muscle in heart failure patients (Dubach et al., 1989; Minotti et al., 1990; Smith, 1991; Sullivan et al., 1988). However, the mechanism underlying the improvements in oxidative capacity are presently not defined. Because evidence from exercise studies using ^{31}Phosporus Nuclear Magnetic Resonance (^{31}P NMR) spectroscopy are consistent with data from histochemical studies, its use in determining the effects of exercise

training on skeletal muscle metabolism may provide further knowledge about the adaptive process in heart failure patients.

Exercise training may not be appropriate for all heart failure patients. Arvan (1988) trained patients with an impaired LVEF for a period of 12 weeks. Although the patients showed a 32% improvement in VO_{2peak}, 5 deaths occurred by one year follow-up underscoring the fact that patients with impaired left ventricular function are at higher risk for complications during participation in rehabilitation programs. Therefore, the question should be raised whether improvements in exercise capacity can be accomplished without having detrimental effects on heart function, or if a reversal of peripheral compensatory mechanisms following training results in a further deterioration of ventricular function (Minotti et al., 1992).

Thus, additional studies should be designed to further describe the adaptive response to training; identify the mechanisms most responsible for these adaptations; determine the interaction of exercise training and pharmacologic therapy; and determine the long-term functional and prognostic outcomes of training in heart failure patients. Furthermore, knowledge regarding the mechanisms of improvement may aid in determining the most appropriate form of exercise training and proper criteria for patient selection.

Purpose of the Study

Thus, there are several pertinent questions which will be addressed in this study in regard to understanding the syndrome of heart failure. However, the two most critical questions that will be addressed in this study are (1) how do the compensatory

adaptations to heart failure respond to an acute bout of exercise and (2) can exercise training provide an adequate stimulus to reverse the compensatory adaptations and improve exercise capacity and tolerance in patients with heart failure?

These questions will be addressed by evaluating the effect of an acute bout of exercise and period of exercise training on central (cardiac function) and peripheral function (neuroendocrine function, and skeletal muscle energetics) in heart failure patients. The principal aims of the research protocol are to assess the effect of both an acute bout of exercise and extended period of exercise training on

I. Cardiac function, as assessed by Doppler echocardiography prior to, during and following an intermittent exercise test.

II. Peripheral function, defined by:

a. neuroendocrine function (fluid regulatory hormones) in response to a symptom-limited maximal graded exercise test (SL-GXT) and

b. skeletal muscle energetics (phosphate metabolism) during and following repetitive submaximal calf flexion exercise using ^{31}P NMR spectroscopy.

III. Functional capacity defined as

a. exercise capacity (VO_{2peak}) and tolerance (exercise time) using an SL-GXT and

b. perception of quality of life, using the Nottingham health profile questionnaire.

Research Hypotheses

The principal hypotheses of the research protocol aimed at evaluating the acute exercise responses in patients with heart failure are the following:

(1) The acute exercise response in heart failure patients will be characterized by a reduced hemodynamic and neurohumoral reserve capacity as compared to age-matched healthy controls.

(2) The reduced reserve capacity will contribute to the marked exercise intolerance in heart failure patients.

(3) The skeletal muscle metabolic responses to acute exercise will be characterized by a decreased oxidative potential in heart failure patients as compared to age-matched controls.

(4) Skeletal muscle recovery kinetics will be prolonged in heart failure patients compared to age-matched controls.

The principal hypotheses of the research protocol evaluating the effects of exercise training on patients with heart failure are the following:

(1) Exercise training will result in an increased hemodynamic and neurohumoral reserve capacity.

(2) Exercise training will result in an increase in functional capacity secondary to reversal of peripheral abnormalities (skeletal muscle energetics and/or neuroendocrine function).

(3) Exercise training will result in enhanced perception of quality of life as evaluated by a standard health profile questionnaire.

Delimitations

This study is delimited to the following:

1) Thirty four volunteer patients with heart failure secondary to ischemic heart disease, based on documented myocardial infarction, and/or cardiac catheterization;

2) Patients with a New York Heart Association (NYHA) classification of II or III, and without significant other disease or contraindications to exercise;

3) Patients ranging in age from 18 to 80 years;

4) Patients with a minimal duration of heart failure of no less than 4 months;

5) Patients consenting not to change diet or physical activity habits during the course of the study; and

6) Patients without cardiac pacemakers or internal defibrillators.

Limitations

This study is limited by the following:

1) Patients received numerous pharmacological agents which may influence cardiovascular and metabolic responses to exercise;

2) Patients did not all receive the same pharmacological agents or respective dose;

3) The duration of heart failure among patients was different which may influence the cardiovascular and metabolic responses to exercise and training;

4) The severity of heart failure among patients was not the same and may influence the responses to the treatment.

Significance of Research

In light of the fact that exercise capacity is a powerful predictor of survival in heart failure patients, reversal of the time-dependent compensatory adaptations associated with heart failure secondary to exercise training could signal improved prognosis. Such information may help physicians develop more appropriate treatment strategies for patients with heart failure. Furthermore, this research could form the background necessary for a mortality study.

CHAPTER 2
REVIEW OF LITERATURE

Introduction

Heart failure develops in response to an insult to the cardiovascular system (Zelis & Sinoway, 1989). This alteration is principally due to three distinct etiologies (Sokolow & McIlroy, 1990) (1) intrinsic myocardial disease secondary to coronary heart disease, cardiomyopathy, and infiltrative disease; (2) excess work load due to increased resistance to ejection (pressure load) secondary to hypertension and hypertrophic cardiomyopathy or increased stroke volume (volume load) secondary to aortic insufficiency and valvular insufficiency; (3) iatrogenic myocardial damage from drugs (doxorubicin and disopyramide) or radiation therapy for mediastinal tumors or Hodgkin's disease.

The insult to the cardiovascular system is frequently met with a variety of compensatory adaptations with short- to long-time constants aimed to maintain cardiac output and arterial pressure to adequately perfuse the brain and the heart. These compensatory adaptations include (1) an increase in ventricular end-diastolic volume and pressure (ventricular dilatation); (2) sympathetic nervous system activation; (3) neurohumoral vasoconstriction; (4) renal sodium and water retention; (5) myocardial hypertrophy; (6) impaired vasodilatory capacity; and (7) intrinsic changes in skeletal muscle. Although, these compensatory adaptations may be remarkably effective under resting conditions, the

capacity to sustain cardiac performance in the face of hemodynamic overload relative to myocardial contractility is finite and exacts a price (Zelis et al., 1991). In fact, it is those compensatory mechanisms that ultimately contribute significantly to the clinical severity of the disease.

The purpose of this review is to describe the compensatory adaptations to heart failure. The focus of the review will be on the morphological, biochemical, cellular, and neurohumoral changes characteristic of heart failure and how these relate to the exercise tolerance, a marker of the clinical severity of the disease.

Compensatory Adaptations to Heart Failure

Cardiac Compensatory Adaptations

Following partial destruction of the myocardium, and/or a pressure or volume overload, the heart uses a series of short- to long-term adaptive strategies to maintain cardiac output compatible with survival. Within seconds to minutes of a reduction in stroke volume, an increase in venous return and inotropic state can cause ventricular dilation and increased myocardial contractility (Ross et al., 1976).

Ventricular dilatation and myocardial contractility

Within seconds to minutes of a reduction in stroke volume due to myocardial infarction, an increase in venous return can cause ventricular dilation (Ross et al. 1976). Ventricular dilatation is the result of adaptive lengthening of the non-infarcted sarcomeres (Pfeffer et al., 1987) or may develop secondary to expansion of an infarcted zone (Hutchins et al., 1978). This adaptive strategy aims to restore cardiac output through the

mechanism (Starling, 1895) despite a loss in contractile function (e.g. a decline in ejection fraction). If the preload reserve is inadequate to maintain cardiac output, activation of the sympathetic nervous system results in an increase in myocardial contractility. Sympathetic activation causes stimulation of beta-receptors and intracellular second messenger systems.

Unfortunately, stretching of the sarcomeres to a more optimal length is an adaptive strategy which is easily pushed to the maximum, increases wall stress (and therefore myocardial oxygen demand), and does not work well chronically (Zelis et al., 1991). In fact, left ventricular dilation (in particular end-systolic volume) represents one of the most powerful prognostic indicators for cardiac failure and death (White et al., 1987). Furthermore, down-regulation or decreased responsiveness of beta-receptors and gradual development of dysfunction of the stimulatory guanylate nucleotide binding protein, which couples the beta receptor to the adenylate cyclase system, and contractile apparatus ultimately renders catecholamine stimulation of the myocardium ineffective (Longabaugh et al., 1988).

Cardiac hypertrophy

To cope with a chronic elevation of myocardial wall stress, the heart must hypertrophy (Zelis et al., 1991). Gradually, new sarcomeres (contractile units) are laid down to share the work load and reduce the wall stress. Data obtained from patients with cardiomyopathies have shown that a reduction in ejection fraction is countered by an increase in left ventricular end-diastolic volume and an almost doubling of left ventricular

mass (Holubarsch et al., 1991). Clearly, such an adaptation has a much longer time constant and is slow in onset and slow to regress. However, myocardial hypertrophy exacts a price. More sarcomeres mean more muscle that needs to be oxygenated which results in an increase in myocardial oxygen demand. The increase in myocardial oxygen demand may subsequently result in myocardial ischemia due to an inability to raise coronary flow beyond the ceiling imposed by coronary artery atherosclerotic obstruction (Pepine & Welsch, 1995).

Summary of cardiac compensations

In summary, the immediate response to a sudden reduction in stroke volume is ventricular dilatation and activation of the sympathetic nervous system to preserve cardiac output. However, these compensatory strategies are often not adequate if myocardial function remains depressed (e.g. following myocardial infarction). In fact, chronic activation of the sympathetic nervous system results in a series of qualitative alterations at the level of the myocyte which may contribute to the deterioration of myocardial function. In an effort to cope with chronic myocardial dysfunction the heart may gradually hypertrophy as evidenced by quantitative changes in muscle mass. This sequence of events may produce a vicious cycle where myocardial failure produces the release of catecholamines which cause an increase in heart rate, contractility, and myocardial oxygen demand, which in turn results in further decompensation of the heart including ventricular dilatation, and myocardial stretch. The myocardial stretch may

serve as a stimulus for further muscle growth and dilatation, and so the vicious cycle continues.

Circulatory Compensatory Adaptations

In patients with low cardiac output, arterial pressure is supported by a rise in systemic vascular resistance (Curtiss et al., 1978). Therefore, in addition to the cardiac compensatory mechanisms discussed above, heart failure is characterized by a complex series of circulatory adaptations which aim to maintain circulatory homeostasis (arterial pressure). These circulatory adaptations, in part secondary to alterations in cardiovascular reflexes, include (1) neural vasoconstriction, (2) humoral vasoconstriction, and (3) local impairment of vasodilatory capacity. Although the compensatory mechanisms may act in concert to maintain arterial pressure, each has its own time-constant and ultimately contributes to the development of the "Heart Failure Syndrome".

Alterations in cardiovascular reflexes

The arterial baroreflexes include an afferent limb, a central neural component, and an autonomic neuroeffector component. A rise in pressure stretches the baroreceptors located in the heart, lungs, and great vessels and causes them to transmit signals to the central nervous system (Guyton, 1996). These signals normally inhibit sympathetic outflow as well as suppress renin and vasopressin release while increasing parasympathetic outflow. Conversely, a sudden reduction in arterial pressure results in a strong sympathetic discharge throughout the body. The short-term effect of the sympathetic discharge is to enhance stroke volume, cardiac output and increase

vasoconstriction in an effort to compensate for a loss in arterial pressure (Osterziel et al., 1990). However, the long-term consequences are thought to be deleterious (Rea et al., 1990).

In the acute phase of low-output heart failure, arterial and cardiopulmonary baroreflexes are activated to help maintain systolic blood pressure. However, both arterial and cardiopulmonary baroreceptors become desensitized in heart failure (Thames et al., 1993). The absence of baroreflex inhibitory input to medullary centers results in excessive sympathetic excitation (Dibner-Dunlap et al., 1992; Eckberg et al., 1971; Ellenbogen et al., 1989). Eckberg et al. (1971) reported impaired baroreflex control of heart rate as assessed by the heart rate response to a bolus intravenous administration of phenylephrine. Other investigators have shown a blunted tachycardic response to a lowering of arterial pressure (Goldstein et al., 1975). It is thought that the marked desensitization of this reflex contributes to the neurohumoral abnormalities (Creager et al., 1986; Porter et al., 1990). These neurohumoral abnormalities will be discussed in greater detail in a later section. Abboud et al. (1981) proposes that in patients with heart failure the abnormalities in the cardiovascular reflexes could lead to a reduced restraining influence on the sympathetic nervous system, thereby removing the restraining or "braking" influence on the heart and circulation. In time, this would favor the development of a neurohumoral excitatory state with tachycardia and sympathetically mediated vasoconstriction.

Alterations in the autonomic nervous system

A rise in systemic vascular resistance is accomplished initially, by activation of the sympathetic nervous system. The effect of systemic activation on the heart was described above. Activation of the sympathetic nervous system is very effective over the short term to maintain blood pressure (Zelis & Flaim, 1982). Arterial norepinephrine concentrations, an index of the activity of this system, is generally two or three times higher in patients with heart failure in comparison to healthy controls (Cohn et al., 1984; Hasking et al., 1986). The magnitude of elevation of plasma norepinephrine is related to the degree of left ventricular dysfunction and carries an ominous prognosis (Cleland et al., 1987; Cohn et al., 1984) The purpose of the increase in sympathetic activation is to maintain cardiac output and arterial pressure through stimulation of myocardial contractility and α-1 adrenoreceptors in the vascular wall. Stimulation of the α-1 adrenoreceptors causes an increase in vasomotor tone and systemic vascular resistance. However, any supportive effect of the increased sympathetic nervous system activity on arterial blood pressure is, in time, superseded by a number of organ-specific consequences. The potential adverse effects of sympathetic activation on cardiac muscle, the kidneys, and the vasculature are numerous and contribute to the clinical manifestations of heart failure (Floras et al., 1993).

Humoral activation

Humoral activation is one of the biochemical hallmarks in patients with heart failure (Drexler, 1991; Hirsch et al., 1987; Kubo et al., 1983). The purpose of the humoral activation is to maintain arterial pressure despite a loss in myocardial function. However, as a result of chronic humoral activation two vicious cycles develop: (1) vasoconstriction and (2) sodium and water retention. Arterial vasoconstriction causes an increase in systemic vascular resistance and inevitably an increase in afterload and systolic wall stress. The sodium and water retention causes an increase in circulating volume, which may be beneficial at first, but ultimately results in an increased ventricular filling pressure and diastolic wall stress. Together, these vicious cycles may eventually lead to progressive myocardial and vascular dysfunction, peripheral tissue abnormalities, fluid accumulation, and finally the clinical picture of heart failure (Remme et al., 1994). The purpose of this section is to review the humoral systems that are involved in the aforementioned process.

Renin-angiotensin-aldosterone system. Renin is synthesized and secreted into the blood by the juxtaglomerular cells located in the macula densa in the afferent arterioles of the glomeruli (Guyton, 1996). Renin, itself, is not a vasoactive substance. Instead it acts on another plasma protein called angiotensinogen, to release a 10-amino acid peptide, angiotensin I (Guyton, 1996). Although angiotensin I has mild vasoconstrictor properties, within a few seconds following its formation two additional amino acids are split to form an 8-amino acid peptide, angiotensin II. The formation of angiotensin II is catalyzed by

angiotensin converting enzyme which is located in the endothelium of the vascular tree (Guyton, 1996). The effects of angiotensin II are multiple and include (1) raising peripheral resistance through vasoconstriction, (2) enhancing renal sodium reabsorption, (3) facilitating catecholamine release from sympathetic nerve endings, and (4) stimulating mineralcorticoid production in the adrenal gland (Hackenthal et al., 1990; Vescei et al, 1978). More recently angiotensin II has also been implicated as a growth factor or growth modulator in the cardiovascular system (Dzau et al., 1981; Paul et al., 1994; Schelling et al., 1991).

Dzau et al (1981) showed that the renin-angiotensin-aldosterone system is markedly activated in patients with decompensated heart failure. Data from the Study of Left Ventricular Dysfunction (SOLVD) Registry report resting values for plasma renin activity in healthy adults ranging from 0.3 to 0.8 (mean 0.6) $ng \cdot ml^{-1} \cdot h^{-1}$ (Benedict et al. 1993). In the same study, plasma renin activity in patients with heart failure ranged from 0.5 to 8.7 (mean 2.5) $ng \cdot ml^{-1} \cdot h^{-1}$ (Benedict et al., 1993). The mechanism of the increased plasma renin activity in heart failure is not entirely known but is thought to be secondary to (1) a reduction in renal perfusion, (2) elevated efferent renal sympathetic nerve activity, (3) increased circulating catecholamines, (4) alterations of sodium load presented to the macula densa, or (5) a combination of all the above (Hirsch et al., 1987; Morali et al., 1991).

As a result of the increased renin-angiotensin-aldosterone system activation systemic vascular resistance increases (Watkins et al., 1976). In addition, the formation

of angiotensin II causes sodium and fluid retention secondary to production of the mineralcorticoid, aldosterone. Aldosterone causes a marked increase in sodium reabsorption from the renal tubules, thereby raising extracellular sodium, followed by fluid expansion. The function of the increased fluid is to increase preload in patients with heart failure secondary to myocardial dysfunction. It is thought that the increase in preload subsequently stretches the sarcomeres in the myocardium to a more optimal length during the intermediate period until myocardial hypertrophy develops.

Angiotensin II could also play an important role in the development of cardiovascular hypertrophy secondary to its vasoconstrictor properties and its mitogenic and growth-promoting effects (Daly & Sole, 1990; Zelis & Flaim, 1982). As a result of its powerful vasoconstrictor properties, angiotensin II, could increase afterload which may eventually give rise to vascular hypertrophy and amplification of neurogenic vasoconstriction (Daly & Sole, 1990; Zelis & Flaim, 1982). Recently, it has been suggested that angiotensin II, may be involved in the adaptive processes in cardiac hypertrophy, atherosclerosis, and myointimal proliferation (Schneider et al., 1989). Izumo et al. (1988) and Schelling et al. (1991) indicated that angiotensin II increased the expression of several nuclear proto-oncogenes such as c-fos, c-myc, c-jun, and of the platelet derived growth factor. Additional studies report that the increased expression of these factors stimulate growth in fibroblast-adrenalcortical cells, vascular smooth muscle cells and cardiac tissue (Dzau et al., 1991; Heagherty et al., 1991; Schelling et al., 1991). With the discovery that the renin-angiotensin-aldosterone system is markedly activated in

heart failure, it is not surprising that a significant number of investigators have focused on the role of angiotensin-converting-enzyme (ACE) inhibitors as a strategy to treat patients with heart failure. Results from subsequent clinical trials have shown convincingly that cardiovascular morbidity and mortality can be reduced in patients with left ventricular dysfunction (ejection fraction $\leq 40\%$) secondary to ischemic heart disease following long-term use of ACE-inhibitors (SOLVD and SAVE). Interestingly, the precise mechanism(s) of action of ACE-inhibitors are still not fully understood. It is thought that the mechanism of action of ACE-inhibition is in part cardioprotective and vasculoprotective. A reduction in systemic vascular resistance secondary to inhibition of angiotensin II generation may reduce afterload and myocardial work. Mechanisms for the vasculoprotective properties include in addition to a reduction in angiotensin II production, decreased bradykinin degradation, antagonism of macrophage function and migration as well as inhibition of sympathetic nervous system and thrombotic activity (Pepine, 1996). All of these could result in plaque stabilization, protection against plaque rupture, and prevention of acute coronary occlusion (Pepine, 1996). Furthermore, the recent indication that ACE-inhibition can reverse structural vascular alterations is promising.

Arginine vasopressin. Arginine vasopressin is a nine amino acid polypeptide which is released by the posterior pituitary and serves to decrease excretion of water by the kidneys (Guyton, 1996). Although the precise mechanism of arginine vasopressin is not fully understood, minute concentrations have been shown to increase the permeability

of the collecting ducts and tubules in the kidney, thereby allowing the reabsorption of water (Montani et al., 1980). In addition, higher concentrations of arginine vasopressin cause marked vasoconstriction in the arterioles throughout the body (Cowley et al., 1984).

From the SOLVD trial, it appears that circulating arginine vasopressin is elevated in heart failure. Benedict et al. (1993) report resting values for patients with heart failure ranging from 1.7 to 3.1 (median 2.4) $pg \cdot ml^{-1}$. This was significantly higher than for healthy normal individuals who ranged from 1.4 to 2.4 (median 1.8) $pg \cdot ml^{-1}$. The mechanism for the release of arginine vasopressin in heart failure is not well understood but is believed to be due to non-osmotic causes (Sztalowicz et al., 1981). Perhaps a decreased sensitivity of atrial stretch receptors, which normally serve to inhibit arginine vasopressin release with atrial distention, contributes to the elevation of circulating arginine vasopressin (Greenberg et al., 1973). Non-osmotic stimulation of arginine vasopressin has been linked to low stroke volume and cardiac output. Improvement in cardiac performance by afterload reduction in patients with heart failure decreases arginine vasopressin levels and enhances water excretion. Plasma arginine vasopressin levels often parallel increases in plasma renin activity (Goldsmith et al, 1983), but may also be affected by baroreceptor stimulation and/or increases in angiotensin II (Uhlich et al., 1975). However, the release of arginine vasopressin is not thought to be a primary mechanism to increase systemic vascular resistance, because of a lack of relationship between arginine vasopressin and left ventricular dysfunction (Benedict et al., 1993).

A potential unfavorable consequence of fluid retention due to elevated arginine vasopressin is hyponatremia. Hyponatremia is a common manifestation of severe heart failure and occurs when water is retained in excess of sodium. It has been shown to be a powerful independent predictor of cardiovascular mortality (Lee et al., 1986).

Atrial natriuretic peptide. Atrial natriuretic peptide is a hormone of cardiac origin and is released in response to atrial distention. The functional role of atrial natriuretic peptide is to preserve cardiorenal homeostasis, by way of sodium balance and inhibition of the renin-angiotensin-aldosterone system. Thus, the action of atrial natriuretic peptide is to decrease plasma volume. Goetz (1988) reported that atrial natriuretic peptide caused a net transfer of fluid from the vascular to the interstitial space. This raises the possibility that atrial natriuretic peptide may have a vascular effect which may contribute to edema formation in heart failure.

Circulating atrial natriuretic peptide levels are reportedly increased in patients with heart failure (Benedict et al., 1993; Burnett et al., 1986; Wei et al., 1993). Data from the SOLVD trial reported resting values for plasma atrial natriuretic peptide in healthy adults from 31 to 64 (median value 48) $pg \cdot ml^{-1}$ versus 54 to 225 (median value 114) $pg \cdot ml^{-1}$ for patients with heart failure (Benedict et al., 1993). The elevation in plasma atrial natriuretic peptide in heart failure patients is thought to be due to increased cardiac volume and/or pressure overload (Burnett et al., 1986; Lee et al., 1989; Suguwura et al., 1988). In acute heart failure the increased levels of atrial natriuretic peptide are secondary to an increase in release of stored atrial natriuretic peptide, whereas in chronic

heart failure increased atrial natriuretic peptide synthesis is thought to maintain the elevated levels (Perrella et al., 1991, 1992).

Several studies have demonstrated that atrial natriuretic peptide correlates with the functional class of patients with heart failure, plasma renin activity, plasma norepinephrine concentrations, and mortality (Davis et al., 1992; Gottlieb et al., 1989). As a result atrial natriuretic peptide has emerged as an important diagnostic and prognostic marker in heart failure (Gottlieb et al., 1989). Using a Kaplan-Meier analysis of cumulative rates of survival in patients with heart failure, stratified into two groups on the basis of median plasma concentration of atrial natriuretic peptide, Gottlieb et al. (1989) found a much higher mortality in those patients with a median plasma concentration greater than 125 $pg \cdot ml^{-1}$. Davis et al. (1992) extended these findings and identified atrial natriuretic peptide as a specific and sensitive test for predicting the development of heart failure in elderly subjects.

Thus, atrial natriuretic peptide is an important counter-regulatory hormone to the renin-angiotensin-aldosterone system and sympathetic nervous system in heart failure. However, recent evidence suggests that there is a diminished response to (Margulies et al., 1991) and a gradual impairment in the capacity to release atrial natriuretic peptide in heart failure (Volpe et al., 1991). The mechanism for the hyporesponsiveness to atrial natriuretic peptide is thought to be multifactorial and include (1) a reduction in renal perfusion (Redfield et al., 1989), (2) increased renal sympathetic nerve activity (Morgan et al., 1989), (3) increased circulating catecholamines (McMurray et al., 1989), (4) atrial

natriuretic peptide receptor downregulation (Schiffrin et al., 1988), (5) enhanced atrial natriuretic peptide enzymatic degradation (Cavero et al., 1990), and/or (6) increased activity of the renin-angiotensin-aldosterone system (Showalter et al., 1988). The impaired capacity to release atrial natriuretic peptide may be the result of chronic volume and pressure overload and inability of the atria to meet the demand of the system (Volpe et al., 1991). Thus, a relative deficiency may develop in patients with chronic heart failure with biologic consequences. It may therefore be hypothesized that the diminished response to and impaired release of atrial natriuretic peptide contributes to the pathophysiology of sodium and water retention and systemic vasoconstriction in patients with heart failure (Brandt et al., 1993).

Alterations in Vasodilatory Capacity

The above mentioned neurohumoral factors can exert potent systemic and regional vasoconstriction in patients with heart failure. However, it is surprising that there is a poor correlation between plasma neurohumoral factors and systemic vascular resistance (Kubo et al., 1990; Levine et al., 1982). This suggests that there are still other factors that modulate vascular tone. Recent studies have identified that in patients with heart failure there is evidence of impaired vasodilatory capacity. For example, LeJemtel et al. (1986) failed to augment maximum limb blood flow following infusion of the α-blocker phentolamine. Moreover, ACE-inhibitors do not restore the vasodilatory response following acute administration, indicating that blockade of the renin-angiotensin-aldosterone system does not result in an immediate improvement in blood

flow to working muscle (Drexler et al., 1989; Wilson et al., 1985). Thus, it appears that there are other mechanisms involved in the impaired vasodilatory capacity of patients with heart failure. There currently are three potential mechanisms, all with long-time constants, which may explain the vasodilatory impairment seen in heart failure: (1) vascular stiffness, (2) vascular deconditioning, and (3) endothelial dysfunction.

Vascular stiffness. Zelis et al. (1970) reported a reduction in maximal vasodilatation in healthy individuals by promoting sodium retention following administration of mineralocorticoids. In heart failure, the chronic elevation of the renin-angiotensin-aldosterone system causes sodium and fluid retention, which may in turn result in an increase in the vascular sodium content. It has been suggested that the increase in vascular sodium and water content leaves the vessels stiff, less responsive to local metabolic stimuli, and may result in a change in the capillary basement membrane morphometry (Derman et al., 1995). Indeed, Sinoway et al. (1987) indicated that approximately one third of the reduced vasodilatory response during exercise in patients with heart failure can be attributed to increased sodium and water content in the vascular wall. They demonstrated an increased muscle blood flow after 24 hours of diuresis. Continued treatment did not improve vasodilatory capacity further, despite an additional loss in body weight. Because peak reactive hyperemia was still markedly below age-matched controls, the authors concluded that sodium and water retention did not completely account for the attenuated vascular responsiveness.

Vascular deconditioning. Chronic vascular deconditioning may also be involved in the impaired vasodilatory capacity of patients with heart failure. Immobilization of the forearm has been shown to reduce vasodilatory capacity (Silber et al., 1990). Conversely, Sinoway et al. (1986) demonstrated that peak vasodilatory capacity in the dominant arms of tennis players was much greater compared to the non-dominant arm. Vascular deconditioning may be secondary to a chronic decrease in blood flow. Sinoway et al. (1988) have also demonstrated a delayed reversal of impaired vasodilatation in patients with heart failure after cardiac transplantation, suggesting the presence of vascular deconditioning. They propose that this may be a deconditioning effect at the arteriolar level, and that it may be related to a hyporesponsiveness to vascular endothelium to generate endothelial-derived-relaxing-factors (EDRFs) in vessels subjected to a chronic low flow state.

Endothelial dysfunction. There is now compelling evidence that endothelium-mediated relaxation is attenuated in both the coronary and peripheral circulation of patients with heart failure (Drexler et al., 1992; Kaiser et al., 1989; Katz et al., 1992; Kubo et al., 1991; Treasure et al., 1993). In patients with dilated cardiomyopathy coronary vasodilatation induced by the endothelium-dependent dilator, acetylcholine is markedly impaired in contrast to only a mild reduction in vasodilatation following infusion of nitroprusside, an endothelium-independent dilator (Treasure et al., 1990). Similar observations have been demonstrated in the peripheral vasculature of patients with heart failure (Olivari et al., 1983).

Kubo et al. (1991) measured forearm blood flow during intra-arterial infusion of methacholine, an endothelium-dependent dilator, and nitroprusside, an endothelium-independent dilator, in patients with heart failure as well as healthy controls. Increases in flow in response to methacholine were significantly depressed in the heart failure patients, whereas flow responses to nitroprusside were similar between the two groups. This suggests an abnormality in the endothelium in the peripheral microcirculation (Kubo et al., 1991). Studies using high-resolution ultrasound have confirmed these previous findings using different endothelium-dependent (e.g. acetylcholine) and -independent (e.g nitroglycerin) dilators (Drexler et al. 1992; Katz et al., 1992). The potential mechanism(s) of endothelial dysfunction are currently unknown, although several hypotheses have been proposed. These hypotheses include (1) alterations in endothelial cell surface receptors, (2) decrease in EDRF synthesis, (3) rapid degradation of EDRF, and (4) increased production of endothelium-derived contracting factors.

Previous studies suggest that the atherosclerotic process selectively affects the endothelial cell surface receptors (Bossaler et al., 1987). Similar findings have been reported in a coronary ligation model of heart failure (Ontkean et al., 1991).

There is no data in heart failure to suggest there are nutritional deficiencies in L-arginine, and/or the cofactors needed in the endothelium-derived relaxing factor production process. However, Miller & Vanhoutte (1988) showed an increase in EDRF synthesis and release as a result of a chronic increase in blood flow. It appears that in a

chronic low flow state, as in heart failure, the reverse could occur and contribute to an impaired ability of the stimulated endothelial cells to produce EDRF.

Rapid degradation of EDRF has been linked to increased oxygen-derived free radical activity. The oxygen-derived free radical superoxide is a known inactivator of EDRF (Rubanyi et al., 1986). Belch et al. (1991) have reported that oxygen-derived free radical production is increased in patients with heart failure. Thus, free radical-mediated inactivation of EDRF in the vasculature of patients with heart failure could contribute to the impaired vasodilatory response (Treasure & Alexander, 1993)

Recent studies have demonstrated a marked increase in plasma Endothelin-1 levels in patients with heart failure (Cody et al., 1992; Stewart, et al., 1990). Endothelin-1 is a known endothelium-derived contracting factor and appears to correlate with indices of the clinical severity of heart failure (Krum et al., 1995; Margulies et al., 1991).

Summary of circulatory compensation

In summary, heart failure is characterized by a complex series of circulatory alterations involving the autonomic nervous system, fluid-regulatory hormones, and vasculature. As a consequence of these circulatory alterations vasodilatory capacity is impaired and systemic vascular resistance markedly elevated in heart failure. Although, the reason for the limited vasodilatation is not fully understood, it could be considered a protective mechanism because it may prevent arterial pressure from decreasing when the failing heart is not capable of increasing cardiac output (Zelis & Flaim, 1982).

Skeletal Muscle Compensatory Adaptations

The result of impaired cardiac pumping capacity and limited vasodilatory capacity is an inadequate blood supply to metabolizing tissues (Sullivan et al., 1989). Thus, a reduction in skeletal muscle perfusion may be an important contributor to the decreased exercise capacity and tolerance in heart failure patients. Yet, even when oxygen availability to skeletal muscle is improved oxygen uptake remains unchanged (Drexler et al., 1987; Marzo et al., 1993; Wilson et al., 1993). This observation suggests the presence of intrinsic alterations of skeletal muscle. Recently, considerable attention has been given to identify those intrinsic alterations in skeletal muscle which may contribute to the clinical severity of patients with heart failure (Caforio et al., 1989; Drexler et al., 1987, 1992; Dunnigan et al., 1987; Lipkin et al., 1988; Mancini et al., 1989, 1992; Marzo et al. 1993; Massie et al., 1987, 1988; Rajagopalan et al., 1988; Sullivan et al., 1990). These studies strongly suggest the presence of skeletal muscle abnormalities including (1) ultrastructural abnormalities, such as significant atrophy of muscle fibers classified as Type I (Caforio et al., 1989; Drexler et al., 1992; Dunnigan et al., 1987; Lipkin et al., 1988; Mancini et al., 1989; Sullivan et al., 1990); (2) a marked decline in mitochondrial enzyme concentration and activity (Succinate dehydrogenase, Citrate synthase and cytochrome oxidase); and (3) a reduction in mitochondrial volume and density (Drexler et al., 1992; Lipkin et al., 1988; Mancini et al., 1989).

Skeletal muscle atrophy

Muscle atrophy is common in patients with heart failure (Caforio et al., 1990; Drexler et al., 1992; Jondeau et al., 1992; Lipkin et al., 1988; Magnusson et al., 1994; Mancini et al. 1989; Minotti et al. 1991; Sullivan et al., 1990). Minotti et al. (1991) found that maximal cross-sectional area of the thigh, measured by magnetic resonance imaging, was markedly reduced in patients with end-stage heart failure compared to age-matched controls. These data have been confirmed by Magnusson et al. (1994) who reported a 13% smaller muscle cross-sectional area of the quadriceps in heart failure patients. Mancini et al. (1992) noted a 15% reduction in muscle volume in the lower legs of patients with mild-to-moderate heart failure. The mechanism for the muscle atrophy in heart failure is presently not clear but has been linked to malnutrition, deconditioning, an increased catabolic state due to sympathetic nervous system hyperactivation, an increase in serum cortisol, corticotropin, and/or tumor necrosis factor (Francis et al., 1990; Levine et al., 1990; Peterson et al., 1988). Thus, it appears that skeletal muscle atrophy could be an important and potentially reversible contributor to exercise intolerance in patients with heart failure. However, it should be noted that parameters of muscle mass only show a weak correlation with VO_{2peak}, suggesting that muscle atrophy contributes only modestly to exercise intolerance in heart failure (Mancini et al., 1992).

Skeletal muscle blood flow

The first study to suggest that skeletal muscle blood flow in heart failure is impaired dates from the 1930s (Weiss & Ellis, 1935). Since then, a number of studies

have confirmed these findings and reported reduced resting blood flow to the arm and leg in heart failure (Sullivan et al., 1989; Wilson et al., 1984, 1985; Zelis et al., 1968, 1975, 1982). On the other hand, Wiener et al. (1986) found no evidence of reduced blood flow at rest in ambulatory, optimally diuresed heart failure patients. Although the reason for these different findings at rest are speculative it may be related to (1) the level of circulatory dysfunction (as described in the previous section), (2) the position in which the measurements were obtained (supine or standing), (3) the amount of muscle atrophy present, and/or (4) the pharmacotherapy of the patient.

Histologic and biochemical alterations in skeletal muscle

It appears that skeletal muscle atrophy in heart failure is selective and more pronounced in the Type I (high-oxidative) muscle fibers. Lipkin et al. (1988) demonstrated atrophy of both type I and II fibers, increased interstitial cellularity, and excess lipid accumulation, in patients with heart failure. Caforio et al. (1989) expanded these findings, reporting abnormalities of skeletal muscle in patients with hypertrophic and dilated cardiomyopathy with evidence of selective atrophy of type I muscle fibers. Mancini et al. (1989) and Sullivan et al. (1990) also demonstrated a relative greater decrease of highly oxidative, fatigue resistant, type I fibers in the calf muscle of patients with heart failure secondary to coronary artery disease. A study by Drexler et al. (1992) further described the shift in fiber type distribution to type II fibers. In this comprehensive study, the authors indicate that because type IIb fibers possess less oxidative capacity than type IIa or even I, a reduction in oxidative capacity could be

attributed to a shift in fiber type distribution. In addition, to these morphologic changes, Sullivan et al. (1990) reported a decrease in the number of capillaries per fibers for type I and type IIa fibers.

The apparent loss in oxidative capacity in heart failure is further evident from studies which have performed biochemical analysis of skeletal muscle. Lipkin et al. (1988) was the first to demonstrate an accumulation of intracellular lipids in heart failure suggesting a possible abnormality in lipid metabolism. Caforio et al. (1989) observed similar increases in intracellular lipid stores and also noted marked reductions in mitochondrial enzymatic activities (succinate dehydrogenase). Sullivan et al. (1990) examined patients with long-standing heart failure and found significant reductions in mitochondrial enzyme concentration for succinate dehydrogenase and citrate synthetase. Furthermore, they found a decrease in 3-hydroxacyl-coenzyme A-dehydrogenase and glycogen content. Drexler et al. (1992) studied a large patient population with heart failure with various etiologies. The study was designed to further define the prevalence and characteristics of skeletal muscle alterations in patients with heart failure and their relation to exercise capacity. Ultrastructural morphometry of muscle biopsies of the vastus lateralis indicated significant abnormalities of skeletal muscle as compared to normals. The volume density of mitochondria and surface density of mitochondrial cristae, markers of structural correlates of oxidative capacity, were significantly reduced by 20% in patients with severe heart failure. Capillary length density was reduced and fiber type distribution of skeletal muscle was shifted to type II fibers. Cytochemical

analysis of cytochrome oxidase activity also revealed significant decreases in heart failure. Both the volume density of mitochondria and surface density of mitochondrial cristae were significantly related to VO_{2peak} and VO_2 at anaerobic threshold, but inversely related to the duration of heart failure. From these studies, it appears that the literature supports the notion that a major component of heart failure is a reduction in oxidative capacity due to intrinsic alterations in skeletal muscle. This reduction in oxidative capacity may play an important role in the clinical syndrome of heart failure by adversely affecting exercise capacity.

Although, the mechanisms for the alterations in skeletal muscle metabolism in heart failure patients are unknown, several factors (neurohumoral, chronic reductions in muscle perfusion, and deconditioning) may be involved (Drexler et al., 1992). Chronic deconditioning may be a key factor in the alterations in skeletal muscle metabolism, since recent studies have shown that physical training can improve exercise capacity in patients with heart failure by delaying the onset of anaerobic metabolism (Dubach et al., 1989; Minotti et al., 1990; Smith 1991; Sullivan et al, 1989). However, chronic muscle underperfusion (at rest or during exercise) and/or increased sympathetic stimulation could also cause many of the above mentioned abnormalities in skeletal muscle metabolism.

Summary of skeletal muscle compensatory changes

In summary, there is convincing evidence that patients with heart failure suffer from a series of skeletal muscle abnormalities which may contribute to the clinical severity of the disease. Skeletal muscle atrophy is often observed in heart failure patients.

Furthermore, histochemical and biochemical findings indicate a marked decrease in oxidative capacity. The mechanism(s) involved in these alterations is (are) not entirely known. Some of the changes appear to be consistent with the effects of bed rest or general deconditioning (Convertino et al., 1982; Coyle et al., 1984; Saltin et al., 1968). However, some of the histologic findings, including alterations in fiber type composition, and decreased capillary density have not been demonstrated in studies involving "healthy" deconditioned individuals. Thus, although the pattern of skeletal muscle alterations is consistent with the effects of deconditioning, there are additional components that may be intrinsic to patients with heart failure.

Summary of Compensatory Changes in Heart Failure

In summary the "Heart Failure Syndrome" is characterized by a series of compensatory mechanisms designed to maintain cardiac output and arterial pressure at a level compatible with life. There are compensatory mechanisms designed to cope quickly with a reduction in stroke volume, and there are mechanisms which operate over a longer period of time. The cardiac compensatory changes include (1) ventricular dilation to stretch the sarcomeres (fast adaptation); (2) ventricular hypertrophy (slow adaptation) and aim to preserve cardiac output. The circulatory changes include (1) autonomic nervous system activation (fast adaptation); (2) humoral activation (intermediate to slow adaptation); (3) impaired vascular responsiveness (slow adaptation), and aim to maintain blood pressure. Alterations in skeletal muscle include (1) skeletal muscle atrophy (slow adaptation) and (2) impaired oxidative metabolism (slow adaptation). Although

speculative, it is thought that those mechanisms with an intermediate to long-time constant eventually contribute to the severe clinical manifestations.

The Role of Exercise in Heart Failure

Traditionally, the management of the heart failure patient includes a combination of pharmacological compounds aimed to relieve clinical symptoms and prolong life. Following initiation of cardiac glycoside, diuretic, and vasodilator therapy many patients experience resolution of their symptoms at rest. However, most patients continue to experience activity-related symptoms, and are often unable to perform many of the normal activities of daily living. Thus, the clinical phase of heart failure includes a marked decline in functional state, as defined by exercise tolerance and capacity with a subsequent decrease in quality of life.

Because the peripheral alterations in heart failure mimic the deconditioning process seen with prolonged physical inactivity, exercise training is slowly emerging as a therapeutic modality for the heart failure patient. Until the late 1980s physical activity for the heart failure patient was discouraged and many patients were told to refrain from physical exertion (Burch & DePasquale, 1966; Dubach et al., 1989; Wenger, 1978). This conservative approach was due to a concern for a greater risk for cardiovascular complications during exercise. Arguably, this conservative approach has contributed to the considerable morbidity in the heart failure patient. The purpose of this section of the review is to examine the evidence which has contributed to the greater emphasis on

exercise training, and to provide a summary of the current recommendations and guidelines for exercise prescription for the heart failure patient.

The Prognostic Value of Exercise Testing in Heart Failure

Cardiopulmonary exercise testing plays a significant role in determining a safe and effective exercise program for healthy persons as well as a variety of patient groups. The purpose of exercise testing is to determine the physiological responses to controlled exercise stress (Lenfant, 1994). Generally, exercise testing of an apparently healthy person is used for the purpose of medical screening; evaluation of exercise capacity; and to provide information for exercise prescription. Exercise testing in a clinical setting can further be used to quantify objectively the functional or clinical significance of the disease; to aid in determining appropriate therapy; to contribute to the prognosis of new clinical events; to help evaluate the effectiveness of various treatment regimens, including surgery, medication, and exercise; and to establish the appropriateness of performing specific job-related, leisure time, or physical conditioning activities (Welsch et al., 1994). Interpretation of exercise test results allows persons with disease to be classified by risk category so that decisions can be made regarding the level of supervision needed during exercise training (American Association for Cardiovascular and Pulmonary Rehabilitation, 1995; American College of Sports Medicine, 1995; American Heart Association, 1992, 1995; Debusk, 1986; Fletcher et al., 1995).

Several investigators have shown that exertional symptom status in patients with heart failure is related to a decline in maximal exercise capacity as defined by the

measurement of oxygen consumption (VO_{2Peak}) (Cohen-Solal et al., 1990, 1995; Franciosa et al., 1984; Sietsema, et al., 1994; Theroux et al., 1979; Weber et al., 1982). Thus, as stated earlier the use of exercise testing in patients with heart failure may also provide valuable information. In fact, the derived information from such tests has been shown to be valuable in the determining the optimal timing of cardiac transplantation (Brooks et al., 1992; Mancini et al., 1991). The measurement of VO_{2Peak} generally shows excellent test-retest reproducibility and may therefore possess the precision to detect small yet clinically significant changes in the clinical status of patients (Fioretti, et al., 1984; Hanson, 1994; Weber, et al., 1982).

In recent years functional capacity has emerged as one of the most powerful predictors of mortality in heart failure (Bittner et al., 1993; Cleland et al., 1987; Cohn et al., 1988; Likoff et al., 1987; Roul et al., 1995; Szlachcic et al., 1985). Szlachcic et al. (1985) were the first to examine the determinants of exercise tolerance and its relationship to prognosis. They followed a group of patients for 12 months after obtaining both rest and exercise hemodynamic measures along with a measurement of exercise capacity assessed during upright cycle ergometry. Patients with a $VO_{2Peak} < 10$ $ml.kg^{-1}.min^{-1}$, severely impaired, had significantly higher mortality (77%) compared with patients with a $VO_{2Peak} > 10$ $ml.kg^{-1}.min^{-1}$ (21%). Data from the SOLVD trial showed that distance achieved in the 6-minute walk test was inversely related to mortality (Bittner et al., 1993). Moreover, they demonstrated that walking distance was also an excellent predictor of hospitalization for heart failure. More recent studies continue to support the

use of exercise testing as a valid and useful predictor of survival (Cleland et al., 1987; Cohn et al., 1988; Likoff et al., 1987; Roul et al., 1995).

The Acute Exercise Response in Heart Failure

Under normal resting conditions, patients with heart failure generally do not exhibit signs or symptoms of their disease. It is not until a physiologic stress, such as exercise, is introduced that the morbidity associated with heart failure becomes apparent. Therefore, the purpose of this section is to review the effects of a single bout of exercise on patients with heart failure. In particular, this review will focus on (1) the cardiac, circulatory and skeletal muscle responses to an acute bout of exercise, and (2) the role each factor may have in limiting the exercise tolerance and capacity of these patients.

Cardiac Responses to an Acute Bout of Exercise

During exercise, cardiac output increases to match the demand for increased blood flow, oxygen and nutrients to the working muscles. The increase in cardiac output during acute exercise can be accomplished through an increase in heart rate and/or stroke volume. In general, patients with heart failure demonstrate characteristic responses to dynamic exercise. However, as functional class declines there is a progressive decrease in peak cardiac output, stroke volume, and heart rate (Hanson, 1994).

Cardiac output is the product of heart rate and stroke volume. It has been shown that the increase in heart rate contributes to cardiac output throughout exercise (Astrand, 1964), whereas stroke volume is thought to be most important during the early stages of exercise (Higginbotham et al., 1986). In healthy individuals cardiac output increases

directly with increasing work levels. This linear relationship is a direct reflection of the demand for increased oxygen supply to the working muscles.

Hickam & Cargill (1947) were the first to show that cardiac output was reduced at any given VO_2 in patients with heart failure. Since then, investigators have consistently shown a close linear relationship between peak exercise cardiac output and VO_{2peak} (Cohen-Solal et al., 1994; Franciosa et al., 1984; Higginbotham et al., 1983; Sullivan et al., 1989; Szlachcic et al., 1985; Weber et al., 1982). Weber et al. (1982) and Sullivan et al. (1989) also indicate that the slope of the increase in cardiac output versus VO_2 is lower in patients with the most severe disability. This finding suggests that the slope of the cardiac output response during a submaximal exercise bout could be an important determinant of exercise capacity.

Stroke volume is determined by four factors (Guyton, 1996) (1) the volume of blood returned to the heart, (2) ventricular distensibility, or the capacity to enlarge the ventricle, (3) ventricular contractility, and (4) aortic and/or pulmonary artery pressure, or the pressure against which the ventricles must contract. Although there are conflicting reports about stroke volume changes during exercise, the traditional thought in healthy individuals suggests that stroke volume increases with increasing rates of work, and seems to level off at approximately 50-60% of maximal capacity (Astrand et al., 1964; Higginbotham et al., 1986). The explanation for the increased stroke volume in healthy individuals is that the Frank-Starling mechanism, defined by an increase in left ventricular end-diastolic volume, operates at lower work rates, whereas an increased

degree of contractility, defined by a decrease in left ventricular end-systolic volume, has its greatest effect at higher work rates.

In patients with heart failure stroke volume is consistently lower at any given work load compared to normals (Weber et al., 1982). Weber et al. (1982) indicated that the stroke volume response to exercise was related to severity of disease as defined by functional class. Using this classification they showed that as functional class declined so did stroke volume at rest. In addition, they indicated that those patients with the most severe impairments lost the reserve capacity to raise stroke volume during exercise. Higginbotham et al. (1987) examined left ventricular volumes at rest and during an incremental exercise test in patients with severe left ventricular dysfunction and healthy controls using right-heart catheterization and simultaneous radionuclide angiography. Results from this study indicated that although stroke volume in patients with left ventricular dysfunction was lower, the relative increase from rest to peak exercise was similar. However, whereas the increase in stroke volume in normals was at least in part due to an increase in the ejection fraction, LVEF in the patient group was unchanged. This suggests an increased role of the Frank-Starling mechanism in the patients with left ventricular dysfunction. In fact, Higginbotham et al. (1987) reported that the patients left ventricular end-diastolic volume increased almost three times as much as the normal subjects during exercise. Thus, it appears that the use of the Frank-Starling mechanism, rather than an increase in contractility, plays an important role in augmenting cardiac output in the face of impaired systolic function.

Recent studies have shown that the mechanism to increase stroke volume during exercise in heart failure patients with diastolic dysfunction is further impaired (Packer et al., 1990). In these patients changes in ventricular relaxation and filling may increase diastolic pressure in the absence of an increase in left ventricular end-diastolic volumes. This indicates that the exercise intolerance in patients with diastolic dysfunction may be secondary to an inability to rely on the Frank-Starling mechanism to increase left ventricular end-diastolic volumes and stroke volume. This has been confirmed in several studies indicating a close association between indices of ventricular filling and exercise tolerance. Sullivan et al. (1989) observed marked increases in left ventricular filling pressures in patients with heart failure without an increase in left ventricular end-diastolic volume suggesting the presence of diastolic dysfunction. These data suggest that in patients with diastolic dysfunction ventricular filling may be attenuated and contribute to a reduction in stroke volume and exercise tolerance.

A reduction in stroke volume at a given work load in patients with heart failure could also be explained by an increase in mitral regurgitation secondary to progressive ventricular dilation. Stevenson et al. (1988) examined stroke counts using radionuclide ventriculography and cardiac output by thermodilution during upright exercise in patients with heart failure due to systolic dysfunction. Calculated mitral regurgitation during exercise was approximately 48%. Following vasodilator therapy calculated mitral regurgitation was significantly less, 21%, and forward stroke volume increased. This suggests that in certain patients with heart failure mitral regurgitation may play a role in

reducing the forward stroke volume with exercise. Vasodilator therapy improves hemodynamics in heart failure at least in part by reducing the detrimental effects of mitral regurgitation. Thus, patients with heart failure appear to rely to a greater extent on the Frank-Starling mechanism to increase stroke volume with exercise. However, as functional class declines, so does the stroke volume reserve. It is thought that this loss in reserve capacity may contribute to the marked impaired exercise tolerance in heart failure.

The increase in heart rate observed during exercise is linear related to the work intensity. In patients with heart failure heart rates at rest and during submaximal exercise are increased, possibly indicating an increased demand on the heart. Cohn & Rector (1988) showed an inverse relationship between resting heart rate and mortality in patients with heart failure. In contrast, peak heart rate (HR_{peak}) responses to an incremental exercise test are generally lower when compared to age-matched healthy normals. This indicates that the heart rate reserve for patients with heart failure is also reduced. The inability to raise the heart rate during exercise is termed chronotropic incompetence (Sullivan & Hawthorne, 1995). The mechanism responsible for chronotropic incompetence in patients with heart failure has been linked to, abnormal reflex control and down-regulation or decreased responsiveness of beta-receptors.

Circulatory Responses to an Acute Bout of Exercise

Autonomic nervous system responses during acute exercise

The sympathetic nervous system has an important role in mediating the response to exercise in healthy individuals (Christensen & Galbo, 1983). During exercise plasma

norepinephrine levels increase in normal subjects, which is thought to be indicative of increased participation of the sympathetic nervous system (Galbo et al., 1975). In contrast, patients with heart failure have much greater rise in plasma norepinephrine levels at submaximal exercise work loads, although at peak exercise, healthy subjects exhibit higher levels of norepinephrine (Francis et al., 1982a, 1982b, 1985). It is generally believed that the rise in sympathetic nervous system with exercise causes blood to be shunted away from non-exercising tissue to working skeletal muscle (Zelis et al., 1974). Although the release of epinephrine and norepinephrine is affected by a variety of factors, plasma levels increase gradually with increasing intensities until approximately 50-70% of VO_{2peak}. At this point plasma levels increase markedly reaching an apex at peak exercise.

During exercise, patients with heart failure exhibit greater-than-normal increases in plasma norepinephrine levels at submaximal workloads than healthy controls (Chidsey et al., 1962; Francis et al., 1982a, 1982b, 1985). It has been speculated that this may result in significant sympathetic vasoconstrictor activity and contributing to muscle underperfusion (Zelis et al., 1974). The increase in plasma levels of catecholamines may reflect an increase in sympathetic nervous activity or a decrease in clearance (Davis et al., 1988; Thomas & Marks, 1978). To test the hypothesis of sympathetic nervous activity hyperactivity microneurography was used to directly record sympathetic nervous activity from intraneuronal recordings (Leimbach et al., 1986). Results demonstrated that patients with heart failure had significant higher resting muscle sympathetic nervous system

activity than age-matched controls (Leimbach et al., 1986). However, the possibility remains that elevated plasma catecholamines could be the result of a decrease in clearance, since it has been shown that an increase in sympathetic nervous activity diminishes renal blood flow. A reduction in renal blood flow may subsequently alter clearance of norepinephrine from plasma to urine (Dimsdale et al., 1991).

Although a number of investigators have observed that sympathetic reflex control of peripheral resistance vessels appears to be impaired in patients with left ventricular dysfunction (Ferguson et al., 1984; Francis et al., 1982a; Goldsmith et al., 1983; Kubo et al., 1983; Wilson et al., 1989), recent evidence raises the possibility that exercise produces considerably less sympathetic vasoconstriction than previously thought (Francis et al., 1985; Wilson et al., 1989). Wilson, et al. (1989) demonstrated that exercise did not produce a major increase in plasma norepinephrine and sympathetic vasoconstriction in ambulatory patients with marked reduced exercise capacity. In fact, blood flow to non-exercising tissue remained unchanged during exercise. Based on this research, Wilson et al, 1989, suggest that patients with heart failure do not develop major redistribution of blood flow from non-exercising beds to working muscle. Thus, the current contention does not necessarily support that the reduced exercise tolerance in heart failure is governed by an activated sympathetic nervous system. Nevertheless, it does appear reasonable to postulate that vasoconstriction mediated in part by the sympathetic nervous system could play a role in limiting skeletal muscle blood flow during exercise in heart failure patients (Zelis & Flaim, 1982).

Humoral responses to acute exercise

As previously described, humoral activation is an important manifestation in patients with heart failure. Persistent neurohumoral activation reflects alterations in cardiovascular control mechanisms that may in part be due to baroreceptor dysfunction (Hirsch et al., 1987; Kubo et al., 1983). However, it is not uncommon for patients recovering from an acute bout of heart failure to have a near normal neurohumoral profile (Dzau et al., 1981). Measurements of plasma hormones at rest may not be adequate to detect any potential abnormalities (Sigurdson et al., 1994). In contrast, humoral abnormalities may be unmasked during times when the cardiovascular system is stressed, such as during physical exercise. Such information may provide the clinician with an opportunity to determine an optimal treatment strategy.

Renin-angiotensin-aldosterone response to acute exercise. Exercise in healthy individuals stimulates the secretion of renin into the circulating blood through sympathetic stimulation of the juxtaglomerular apparatus and via several other mechanisms such as sweating (Staessen et al., 1987; Tidgren et al., 1991). The magnitude of the renin response to exercise is related to the intensity of exercise and occurs rapidly and is short-lived (Kotchen et al., 1971). Kotchen et al. (1971) reported a significant increase in renin activity following exercise at 70% of VO_{2peak} and at 100% of VO_{2peak}, but not after 40% of VO_{2peak}, indicating a curvilinear response. Baseline values for healthy individuals are generally low and in the range of 0.5 to 1.5 $ng \cdot ml^{-1} \cdot hr^{-1}$ and

increase 4.0 to 6 fold during high intensity exercise (Convertino et al., 1983; Kotchen et al., 1971; Staessen et al., 1987).

In patients with heart failure there is evidence of increased activity of the renin-angiotensin-aldosterone system at rest (Curtiss et al., 1978; Kirlin et al., 1988; Wilson et al., 1989). Plasma renin activity reportedly rises abnormally in heart failure (Wilson et al., 1989). Wilson et al. (1989) reported plasma renin activity in heart failure markedly higher during exercise, reaching at peak exercise 44.5 ± 13.3 $ng \cdot ml^{-1} \cdot hr^{-1}$ versus only 1.0 $ng \cdot ml^{-1} \cdot hr^{-1}$ in healthy normal controls. Kirlin et al. (1988) observed a similar pattern in their study. It would seem that such an increase in plasma renin activity could result in a significant increase in angiotensin II to augment systemic vascular resistance.

Sigurdsson et al. (1994) reported significant increases in plasma ACE activity with maximal exercise in patients with heart failure. Following 12 weeks of ramipril therapy resting values of ACE activity was reduced, although the relative increase with exercise was not blocked. Increased angiotensin II levels following exercise were recently reported by Sigurdsson et al. (1994). Plasma values for angiotensin II, converting enzyme activity, and aldosterone were within normal limits at baseline and all increased significantly with exercise. The authors reported a large variation in angiotensin II levels among patients, although those patients with the lowest exercise times had the greatest increase in angiotensin II after maximal exercise.

Interestingly, inhibition of the converting enzyme does not translate to improved blood flow to skeletal muscle (Drexler et al, 1989). Moreover, exercise tolerance and leg

muscle perfusion remain unchanged with acute administration of angiotensin converting enzyme inhibitors in patients with heart failure (Drexler et al., 1989; Wilson et al., 1985). In contrast, long-term ACE-inhibitor therapy does improve regional blood flow and exercise tolerance in patients with heart failure (Drexler et al., 1989). Thus, the impact of the activated renin-angiotensin-aldosterone system on exercise capacity and tolerance in patients with heart failure remains elusive. In heart failure patients, it is speculated that the marked increase in plasma renin activity and subsequent angiotensin II activity augments systemic vascular resistance in an attempt to maintain arterial blood pressure, despite the cardiac pump dysfunction.

Arginine vasopressin response to acute exercise. Although, there are several studies that have evaluated the effect of exercise on plasma arginine vasopressin concentrations (Convertino et al., 1980, 1981, 1983; Wade et al., 1980, 1987), there is only one study that has done so in patients with heart failure (Kirlin et al., 1986). Convertino et al. (1980) investigated the interrelationships of plasma volume, osmolality, arginine vasopressin, and plasma renin activity to graded workloads in an acute bout of cycle ergometer exercise and following a training period. The results from the acute exercise study indicate that the loss of plasma volume from the vascular space and the increased osmolality induced by increasing exercise intensities were associated with proportional increases in plasma arginine vasopressin (Convertino et al., 1981). Wade et al. (1980) reported a linear relationship between graded exercise and arginine vasopressin concentrations. Kirlin et al. (1986) has reported the only study which has evaluated the

effect of exercise on plasma arginine vasopressin in heart failure. In this study, arginine vasopressin responses were determined during two submaximal cycle ergometer workloads (50 watts and 100 watts). Plasma arginine vasopressin concentrations did not change significantly in patients with heart failure (3.5 to 4.0 $pg \bullet ml^{-1}$), but rose in healthy subjects from resting levels (0.5 $pg.ml^{-1}$) to levels comparable to the resting levels of the patient group (2.0 $pg \bullet ml^{-1}$) (Kirlin et al., 1986).

Atrial natriuretic peptide response to acute exercise. Plasma atrial natriuretic peptide concentrations are increased in both healthy persons and heart failure patients during an acute bout of exercise (Mannix et al., 1990; Saito et al., 1987; Tanaka et al., 1987). However, the precise kinetics of atrial natriuretic peptide production during exercise are not firmly established.

As previously discussed, basal levels of atrial natriuretic peptide are increased in patients with heart failure. Keller et al. (1988) and Petzl et al. (1987) reported significant increases during an acute bout of exercise and contributed this rise to increases in left atrial pressure. Other studies, however, have reported a response comparable to normals (Donkier et al. 1991), or a relatively blunted response, especially in patients with more severe disease (Nicholls et al., 1992; Raine et al., 1986). Although, the blunted response is not clearly understood, it is thought to be the result of cardiac myocyte depletion and/or a mere reflection of the lower exercise levels achieved.

Vascular responsiveness during an acute bout of exercise

During acute exercise the ability of the peripheral vasculature to dilate plays an important role in determining blood flow to exercising muscle. The ability to dilate the vasculature is largely dependent on the integrity of the vascular wall, including the endothelial lining. There are several studies that have evaluated the effects of exercise on blood flow in heart failure. However, it is surprising that few studies have directly assessed the effects of an acute bout of exercise on the vascular response in heart failure.

It is well established that the diameter of a blood vessel is influenced by a variety of factors including changes in blood flow. It is hypothesized that the increase in blood flow through a vessel causes a change in the shear stress on the vascular wall. An increase in shear stress, as seen during a period of reactive hyperemia, is a potent stimulator of the endothelial lining resulting in release of nitric oxide. Nitric oxide accounts for the biological activity of EDRFs. Preliminary observations from this laboratory in healthy normal adults indicate that the vasodilatory response is directly related to the intensity of the signal causing the reactive hyperemia. For example, a 5 minute period of forearm ischemia results in a 10% increase in the diameter of the brachial artery (Welsch et al., 1995). When ischemia and exercise are combined a 17% increase in brachial artery lumen size was seen (Welsch et al., 1995).

In contrast, the vasodilatory response to increased shear stress is markedly abnormal in patients with heart failure (Drexler, et al., 1992; Jondeau et al, 1993; Kubo, et al., 1991). Welsch et al. (1995) used high resolution ultrasound to determine brachial

artery diameter and flow-velocity at rest, during reactive hyperemia (endothelium-dependent), and after nitroglycerin (endothelium-independent vasodilatation) administration, in 9 heart failure patients. Endothelium-dependent vasodilatation was determined following 5 min of forearm ischemia and 3 min of repetitive contractions during ischemia. There was no evidence of endothelium-dependent vasodilatation following ischemia or exercise and ischemia combined, despite a significant increase in the flow velocity signal. Yet, nitroglycerin induced vasodilatation in all heart failure patients. Jondeau et al. (1993) linked the impaired endothelium-dependent vasodilatation to exercise capacity, and found a strong correlation between peak hyperemic response and VO_{2peak} in patients with heart failure. Thus, these data suggest that patients with heart failure exhibit an impairment in endothelium-dependent vasodilatation following exercise induced hyperemia, which may contribute to the exercise intolerance.

Skeletal Muscle Responses to an Acute Exercise Bout

Skeletal muscle strength

Lipkin et al. (1988) measured muscle strength in patients with severe heart failure and found a 45% reduction in quadriceps strength compared to age-matched controls. Magnusson et al. (1994) also observed low muscular strength in patients with heart failure and attributed the reduced strength to a smaller muscle cross-sectional area. In contrast, Minotti et al. (1991) found no difference in isometric strength between heart failure and controls, although there was evidence of a marked decline in muscular endurance. This suggests that the specific tension (i.e. tension per unit of cross-sectional

area) may not be altered as a result of the disease. Buller et al. (1991) confirmed this finding showing no difference in maximal force produced during 3 repetitions, but a marked decline in force production during prolonged knee extension exercise in heart failure. In both studies the degree of muscle dysfunction as defined by muscle endurance, correlated with VO_{2peak} as measured by cycle ergometry (Buller et al., 1991; Minotti et al., 1991). Thus, reduced muscle strength in patients with heart failure is probably due to skeletal muscle atrophy, rather than a change in the contractile apparatus. In contrast, the impaired muscle endurance appears to reflect a qualitative change in skeletal muscle.

Skeletal muscle blood flow during an acute bout of exercise

As previously stated a number of studies have reported reduced limb blood flow at rest in heart failure (Zelis et al., 1968, 1975, 1982). In addition, there is substantial evidence that the increase in blood flow to working muscle is attenuated for each given workload in heart failure (Sullivan et al., 1989; Wilson et al., 1984, 1985; Zelis et al., 1968, 1975, 1982). Wilson et al. (1984) have consistently found reduced leg blood flow during submaximal and peak exercise in patients with heart failure using the thermodilution technique. Sullivan et al. (1989) have confirmed these findings and found a strong relationship between the leg blood flow response to exercise, and VO_{2peak} and functional class.

The failure of skeletal muscle blood flow to increase normally during exercise appears to be primarily related to an impaired vasodilatory capacity. In patients with heart failure, arteriolar vasodilatation is impaired, as evidenced by a failure of leg

vascular resistance to decrease normally with exercise (LeJemtel et al., 1986; Sullivan et al., 1989; Wilson et al., 1984; Zelis & Flaim, 1982). Zelis & Flaim (1982) were the first to describe a 'stiffness factor' in skeletal muscle resistance vessels even when presented with an intense metabolic vasodilator stimulus. The mechanisms involved in the impaired metabolic vasodilatory capacity within skeletal muscle in heart failure include (Zelis et al., 1988a) (1) excessive sympathetically mediated vasoconstriction, (2) increased levels of angiotensin II and vasopressin, (3) chronic vascular deconditioning, and (4) endothelial dysfunction. Each of these mechanisms have been described in detail in different sections of this review.

Another explanation for the alterations in skeletal muscle perfusion observed in heart failure patients may be related to the distribution of blood during exercise. It is generally accepted that exercise is associated with an increase in sympathetic vasoconstrictor activity and angiotensin II (Fagard et al., 1977; Kotchen et al., 1971). This increase in neurohumoral activation serves to increase vascular resistance in non-working tissue and helps to increase arterial blood pressure. On the other hand local metabolic dilators override the neurohumoral influence in working tissue, thereby, allowing a redistribution of blood to exercising muscle (Rowell, 1974). In contrast, Wilson et al. (1989) noted that patients with heart failure do not develop major re-distributions of blood flow from non-exercising beds to exercising muscle. The mechanism for the failure to shunt blood to working tissue was attributed to a reduced sympathetic vasoconstrictor activity. Certainly, this hypothesis appears to go in the face

of traditional views, suggesting that increased sympathetic nervous system activity enhances vasoconstriction in heart failure.

Irrespective of the precise mechanism, the above studies provide convincing evidence that skeletal muscle perfusion is altered in heart failure patients during exercise. It is therefore not surprising that exertional fatigue in heart failure has traditionally been attributed to muscle underperfusion (Sullivan et al., 1988; Zelis et al., 1968, 1974).

Skeletal muscle metabolic responses to acute exercise

There is convincing evidence that skeletal muscle metabolic responses to an acute exercise bout in heart failure are abnormal. Using ^{31}P NMR spectroscopy, exercise studies of forearm and leg musculature have shown that intracellular pH and phosphocreatine (PCr) concentrations are lower and concentrations of inorganic phosphate (Pi) higher at any given workload in patients with heart failure. This pattern indicates greater acidification and the early onset of anaerobic metabolism of skeletal muscle during exercise. It appears that these metabolic alterations are independent of skeletal muscle blood flow. There are three studies demonstrating a greater increase in the Pi to PCr ratio (Pi/PCr), a measure of oxidative stress, and more pronounced drop in pH during progressive forearm exercise in heart failure compared to healthy controls despite similar forearm blood flows (Minotti et al., 1990; Wiener et al., 1986; Wilson et al., 1985). Arnolda et al. (1990) studied blood flow and the metabolic response to exercise in the gastrocnemius muscle. In this study, the PCr/(PCr+Pi) ratio was lower in patients with heart failure at the same relative workload, even though muscle pH and

blood flow were similar to healthy controls. Massie et al. (1988) further explored the metabolic responses in exercising muscle under ischemic conditions. In this study, it was demonstrated that skeletal muscle metabolic responses of the flexor digitorum were still markedly different in heart failure patients, when exercise was performed with a cuff sphygmomanometer inflated to 250 mmHg. These data indicate an increased reliance on anaerobic glycolytic metabolism and decreased oxidative phosphorylation during exercise in skeletal muscle in heart failure compared to controls.

In addition to the above-mentioned skeletal muscle metabolic abnormalities observed during exercise, there is evidence of impaired PCr resynthesis (PCr_{res}) after exercise in heart failure patients (Chati et al., 1994; Cohen-Solal et al., 1995; Mancini et al., 1992; Massie et al, 1987). The measurement of PCr_{res} after exercise provides an index of the oxidative capacity of the muscle, independent of workload, provided that pH does not change significantly (Mahler, 1985; McCully et al., 1990; Meyer, 1988). Cohen-Solal (1995) linked the slow recovery kinetics of PCr to the prolonged postexercise recovery of VO_2, and found a linear correlation. This may have implications for understanding the symptoms reported by heart failure patients after repeated submaximal efforts during their daily activities.

It certainly appears that the metabolic responses observed during and following exercise in heart failure are a result of chronic deconditioning. However, as previously described, there are certain skeletal muscle adaptations and responses that may be intrinsic to patients with heart failure. Early acidification within skeletal muscle may

result in a feedback signal to higher brain centers, which respond by inducing a shutdown of the muscle's mechanical performance, thereby reducing the oxygen demand. The metabolic shutdown in skeletal muscle would eventually reduce the demand on the failing heart (Zelis & Flaim, 1982).

Summary of the Acute Exercise Response in Heart Failure

In recent years exercise capacity has emerged as one of the most powerful predictors of mortality in heart failure (Bittner et al., 1993; Cleland et al., 1987; Cohn et al., 1988; Likoff et al., 1987; Roul et al., 1995; Szlachcic et al., 1985). Nearly all patients with heart failure suffer from rapid onset fatigue that results in a markedly reduced exercise capacity. Yet, the physiologic responses to an acute bout of exercise in heart failure are, for the most, characteristic to those observed in healthy normals. Close examination of cardiac and circulatory responses in heart failure do reveal a marked decreased reserve capacity from pre-exercise to maximal exercise conditions. For example, patients with heart failure demonstrate a characteristic cardiac response to dynamic exercise. However, as functional class declines there is a progressive decrease in peak cardiac output, stroke volume, and heart rate (Hanson, 1994). Similarly, the capacity to raise skeletal muscle blood flow during exercise is reduced, secondary to changes in neurohumoral and vascular responsiveness. It is thought that the decreased reserve capacity in cardiac output, stroke volume, heart rate, and vascular responsiveness contribute to the reduced skeletal muscle blood flow and impaired exercise tolerance in patients with heart failure. Additional factors that contribute to the early onset of fatigue

in heart failure are an increased reliance on anaerobic metabolic pathways, and impaired oxidative metabolism of skeletal muscle.

Thus, the exercise intolerance characteristic of heart failure patients appears to be related to a change in oxygen and nutrient delivery to the musculature, as well as a reduced oxidative capacity of skeletal muscle. Although, several of the above-mentioned factors could be linked to a deconditioning process, other theories should be considered. One theory suggests that the limited vasodilatation is an attempt to prevent excessive hypotension, when the failing heart is not capable of further increasing cardiac output during exercise (Zelis & Flaim, 1982). A second theory proposes that the impaired muscle performance is an attempt to protect the cellular environment from excessive damage during ischemic conditions (Gorman et al., 1988).

The Response to Exercise Training in Heart Failure

The first report indicating that heart failure patients could safely participate and benefit from a cardiac rehabilitation program dates to 1979 (Lee et al., 1979). In this study, 18 post myocardial infarction patients, with an average LVEF of 18% were trained at 70% to 85% of their maximal heart rate for 20 to 45 min, 4 days per week. The average training program was 19 months and resulted in an increased exercise tolerance, as defined by treadmill exercise time (Lee et al., 1979). Since that study, an additional five non-randomized studies (Arvan, 1988; Baigrie et al., 1992; Conn et al., 1982; Jugdutt et al., 1988; Sullivan et al., 1988), and only three randomized trials (Coats et al., 1990, 1992; Jette et al., 1991) have been conducted. Although, there is considerable variation

in the duration, intensity and length of training in these studies, a consistent finding is that heart failure patients can increase exercise capacity and tolerance following a period of exercise training without increasing the risk for cardiovascular complications. The increase in VO_{2peak} and exercise time, as reported by these studies, ranges from 1.4 $ml.kg^{-1}.min^{-1}$ (Baigrie et al., 1992) to 7 $ml.kg^{-1}.min^{-1}$ (Arvan, 1988), and 1.1 min to 4.0 min, respectively. Yet, despite these consistent findings, the mechanism of the training response in heart failure is not fully understood. However, it appears that the improvements in exercise capacity are more related to reversing the peripheral compensatory abnormalities, rather than improvements in cardiac function.

Cardiac Responses to Exercise Training in Heart Failure

Cardiac output shows either no change (Sullivan et al., 1988), or a small increase (Coats et al., 1992) following a period of chronic exercise training. In the study by Sullivan et al. (1988) patients exercised approximately 60 min, 3-5 days/wk at 75% of peak HR_{peak}. Although, there was a trend toward an increase in maximal exercise cardiac output, indices of left ventricular function did not change (Sullivan et al, 1988). On the other hand, in a randomized cross-over trial by Coats et al. (1992) exercise training was associated with an increase in both submaximal and maximal cardiac output during exercise in eleven patients with mild to moderate ischemic heart failure. The increase in peak cardiac output was in large due to changes in stroke volume, and was achieved at a greater absolute work load. The apparent differences between these studies are difficult to interpret, but could be a function of several factors such as (1) etiology, severity and

duration of disease, (2) training modality and intensity, (3) length of the training program, (4) method of cardiac evaluation, or (5) a combination of all the above.

Thus, Coats et al. (1992) is the only study to report an enhanced stroke volume response to exercise following training. This study showed that the training-induced increase in cardiac output during supine submaximal exercise was largely due to an increase in stroke volume as the heart rate response did not change. The increase in cardiac output at peak exercise was in part a result of an increase in HR_{peak}. It is not known if the enhanced stroke volume represents improved venous return, diastolic relaxation and recoil, increased left ventricular mass, and/or contractile performance. The study also did not provide evidence whether exercise resulted in an increased end-diastolic volume, decreased end-systolic volume, or both.

Perhaps one of the most consistent response to exercise training is a reduction in resting heart rate and at any given submaximal workload (Clausen, 1976). The reduction in resting heart rate is thought to reflect a change in the balance between sympathetic and parasympathetic activity towards greater dominance of the vagal nerve. The reduction in heart rate during exercise is, generally, attributed to a larger stroke volume, secondary to myocardial hypertrophy (Clausen, 1976) or an increase in blood volume (Holmgren et al., 1960). In the study by Sullivan et al. (1988) and Coats et al. (1990) resting and submaximal exercise heart rates also decreased in patients with heart failure following training. Furthermore, a slight but significant increase in HR_{peak} was observed by Coats et al. (1990). These findings may be particularly intriguing since both an elevated heart

rate at rest (Cohn et al., 1988) and chronotropic incompetence (Colucci et al., 1989; Higginbotham et al., 1983; Weber et al., 1982) are factors affecting exercise performance and survival in patients with heart failure.

There has been no evidence of any improvement in left ventricular function, as defined by LVEF, in patients with heart failure following training (Jette et al., 1991; Jugdutt et al., 1988; Lee et al., 1979; Sullivan et al. 1989). In fact, Jugdutt et al. (1988) recently reported a significant deterioration in both global and regional function in patients with marked left ventricular asynergy (>18%, indicating a substantial infarction) following training. Other studies have not confirmed these findings (Giannuzzi et al., 1993, Jette et al., 1991). Giannuzzi et al. (1993) used a multicenter randomized trial to determine the effect of exercise training on left ventricular remodeling in patients status post anterior myocardial infarction. The exercise training program consisted of an aggressive 6-month stationary cycling and walking program. Although, patients with an ejection fraction <40% had more significant ventricular enlargement before and after training, the exercise group did not appear to have any greater deterioration. Thus, the authors of this study concluded that postinfarction patients without clinical complications could benefit from long-term training without additional negative effects on ventricular size and topography. Nevertheless, because the subset of patients with an ejection fraction <40% represented only 33% of the total study group, larger clinical trials are necessary to confirm these results.

Circulatory Responses to Exercise Training in Heart Failure

Exercise training and the autonomic nervous system

The effects of exercise training on resting and exercise sympathetic and fluid-regulatory hormone concentrations are scarce for both healthy normals and patients with heart failure. In healthy adults exercise training has been associated with a decrease in sympathetic nervous system activity as evidenced by a decrease in plasma norepinephrine (Kiyonaga et al., 1985). Noakes et al., (1983) reported that exercise training resulted in an increase in the "trigger" threshold for ventricular fibrillation in normoxic, hypoxic and ischemic rat hearts. Although the mechanism for the increase in the "trigger" threshold was not clear a reduction in plasma catecholamines, secondary to a reduction in the sympathetic nervous system activity, could have played an important role (Noakes et al., 1983). Coats et al. (1992) evaluated the autonomic control of the circulation following training in patients with heart failure using (1) RR variability, (2) power spectral analysis, and (3) whole-body radiolabeled norepinephrine spillover. Each of these markers of autonomic function showed a significant shift away from sympathetic activity toward enhanced vagal tone (Coats et al., 1992).

Exercise training and the humoral system

There currently are no studies which have reported on the effects of exercise training on the fluid-regulatory hormones. Clearly, future studies are needed to determine if exercise training results in reversing the humoral activation present in many patients with heart failure.

Exercise training and the vascular system

Hornig et al. (1996) are the first to suggest that a local exercise program can enhance vasodilatory capacity in patients with heart failure. In this cross-over trial, patients participated in 4 weeks of training which consisted of handgrip exercise at 70% of peak handgrip strength for 30 min per day. Exercise training restored flow-dependent dilation in patients with heart failure. This data suggests an enhanced endothelial release of nitric oxide. It should be noted that the beneficial effect of training was specific to the area trained and was lost after 6 weeks of cessation of training (Hornig et al., 1996). Future studies should address the impact of exercise training on restoring normal endothelial function in the coronary vasculature.

Clearly much work needs to be done to determine the role of exercise training in neurohumoral function in heart failure. However, the early data from Coats et al. (1992) and Hornig et al. (1996) suggests that exercise training may contribute to reversing the abnormalities in autonomic function, and restore endothelial function in patients with heart failure.

Skeletal Muscle Responses to Exercise Training in Heart Failure

Exercise training and skeletal muscle strength

Resistance training has not been advocated for patients with heart failure because of the concerns about potential adverse hemodynamic responses. Therefore, there currently is no data that has evaluated the effects of resistive exercises on muscle strength in patients with heart failure. Recently, a randomized, controlled, single blind trial,

Exercise Rehabilitation Trial in Congestive Heart Failure was initiated to examine the short- and long-term effects of a combined aerobic and resistance training program in patients with heart failure (McKelvie et al., 1995).

Exercise training and skeletal muscle blood flow

There is evidence from both human and animal studies that exercise training may improve skeletal muscle blood flow (Armstrong et al., 1984; Laughlin et al. 1987; Sullivan et al., 1988). Sullivan et al. (1988) reported significant improvements in peak leg blood flow and $(a\text{-}v)O_2$ difference in heart failure patients with significantly reduced LVEF (24%), following 4-6 months of exercise training. The exercise prescription during this training protocol consisted of approximately 60 min of cardiovascular activity performed 3-5 days/wk at 75% of HR_{peak}. The improvement in skeletal muscle blood flow is not related to improved central hemodynamics and appears to be directly related to exercise capacity (Drexler et al. 1989; Sinoway et al, 1986).

Exercise training and skeletal muscle metabolism

Three studies have reported on the ability of skeletal muscle to significantly improve metabolic capacity following exercise training in patients with heart failure (Adamopoulos et al., 1992; Minotti et al., 1990; Stratton et al., 1994). Minotti et al. (1990) examined the ability of skeletal muscle to adapt in patients with a mean LVEF of 27%. Patients participated in a 28-day localized unilateral forearm training program. Training consisted of multiple sets (8 min in duration) of wrist flexion exercise performed 6 days/week. Following training, muscle bioenergetics, as assessed by ^{31}P-NMR

spectroscopy, improved in the trained forearm, whereas muscle mass, limb blood flow and cardiac output remained unchanged. In addition, the authors reported an impressive 260% increase in muscle endurance measured as the number of minutes that a submaximal load could be lifted until exhaustion. Results from a similar protocol by Stratton et al. (1994) further extended Minotti's data. In this study patients with mild heart failure also participated in a one month forearm training protocol. Following training there were significant improvements in skeletal muscle responses to exercise with lesser PCr utilization, higher muscle pH at submaximal workloads, and improvement in PCr_{res}, which is also an indicator of mitochondrial ATP synthesis rate. Adamopoulos et al. (1992) studied calf muscle metabolism, using ^{31}P NMR spectroscopy, during an acute exercise bout, before and after 8 weeks of training. The major findings of this study included a reduction in PCr depletion, and an enhanced rate of PCr_{res} in recovery. Combined, these findings suggest that skeletal muscle abnormalities in heart failure are, in part, due to a deconditioning process, and can be partially reversed through exercise training.

Summary of the Response to Exercise Training in Heart Failure

Thus, there is growing evidence that exercise training may reverse many of the peripheral abnormalities present in the heart failure patient. Exercise training may improve autonomic function, skeletal muscle blood flow and localized oxidative capacity. Together, these changes may translate in an increased exercise tolerance, reduction in activity-related symptoms, and improved quality of life. These findings assume added

importance in light of previous reports that exercise capacity is the most powerful predictor of survival of heart failure patients.

Whether exercise training can improve long-term functional and prognostic outcomes in heart failure patients is presently uncertain. However, there is some evidence from experimental models that exercise training can increase the threshold for ventricular fibrillation (Noakes et al., 1983). Furthermore, the improvement in exercise tolerance in heart failure patients following training equals that achieved in controlled trials of ACE-inhibitors (Coats, 1993). Finally, since exercise tolerance is known to be an independent marker of prognosis, an increased exercise capacity following training may itself indicate a prognostic benefit.

Guidelines, Risk Stratification, and Exercise Prescription of the Heart Failure Patient

In the last year the American Heart Association (AHA), the American College of Sports Medicine (ACSM), the American Association for Cardiovascular and Pulmonary Rehabilitation (AACVPR) and the Center for Disease Control have all come out with updated guidelines, standards and statements on exercise (American Association for Cardiovascular and Pulmonary Rehabilitation, 1995; American College of Sports Medicine, 1995; Fletcher et al., 1995; Pate et al., 1995). Each organization strongly encourages the stratification of individuals in risk categories prior to engaging in a physical activity program. These risk categories should be based on the individuals clinical characteristics and likelihood of untoward events. The AHA recommends the use of the following categories to classify individuals prior to starting an exercise program

(Fletcher et al., 1995): Class A, Individuals with no evidence of increased cardiovascular risk for exercise, Class B, Patients with known, stable cardiovascular disease with low risk for vigorous exercise but slightly greater than for apparently healthy individuals, Class C, Patients at moderate to high risk for cardiac complications during exercise and/or unable to self-regulate activity or to understand recommended activity level, Class D, Patients with unstable disease and activity restrictions.

Using these risk strata the AHA recommends that medically stable heart failure patients may participate in exercise training programs (Fletcher et al., 1995). Typically, the majority of stable heart failure patients will be classified as Class C patients, however, a significant number of patients with mild heart failure may be classified as Class B based on their clinical characteristics (e.g. Exercise capacity > 6 METs, LVEF between 40%-60%). This may suggest that some heart failure patients could qualify for a comprehensive rehabilitation program including light to moderate resistance training. Regardless of the classification, the exercise program should be individualized and medical supervision provided until safety is established (Fletcher et al., 1995).

To date all published exercise training studies in heart failure patients have been performed on medically stable patients (Coats, 1993). No studies have been performed on patients with a functional capacity less than 14 $ml.kg^{-1}.min^{-1}$ or 4 METs, NYHA class IV patients, or patients with other indicators of poor prognosis. There are no published criteria for a minimal LVEF for exercise training, which is not surprising as LVEF is an unreliable predictor of exercise capacity.

Prior to starting the program a clear understanding of the patient's medical history, present medical and physiological status, and personal need is necessary to maximize safety and efficacy (Pollock & Schmidt, 1995; Welsch et al., 1994). Once the heart failure patient is deemed medically stable, and fluid status is adequately controlled, the patient should be introduced to an exercise training program. The exercise prescription should have specific guidelines concerning the frequency, intensity, duration, mode, and progression of the exercise program (Welsch et al., 1996). Initially, because of the marked exercise intolerance, it may be necessary to use an interval training approach, with 2-6 min low level activity interspersed with 1 to 2 min rests. Frequency of training may be as much as 2 to 3 times a day during the early stages of the program. Warm-up and cool-down periods should be longer to allow adequate time for the body to prepare and recover from the activity. Depending on the patient's medical status, reported symptoms during training, and tolerance of the exercise session, intensity, duration and frequency may be altered. Determination of an appropriate exercise intensity for the heart failure patient should be based on VO_{2peak}, secondary to frequent impaired chronotropic responses. A starting intensity of 40-60% of VO_{2peak}, or 10 beats below any significant symptoms, such as angina, exertional hypotension, dysrhythmias, and shortness of breath is recommended. More constant supervision may be needed during the early stages of the exercise program for all heart failure patients. The use of more intensive monitoring of blood pressure responses and electrocardiograms should be considered in those patients deemed at higher risk (AHA: Class C). Rating of perceived exertion should range from

11-14 (on the 15-grade category Borg scale), whereas symptoms of angina and dyspnea should not exceed 2+ on a "0-4" scale ("Moderate, Bothersome" on the Angina scale and "Mild, Some Difficulty" on the Dyspnea scale). The duration of exercise should be gradually increased to 30 min depending on patient's tolerance. The choice of exercise should be activities that are predominantly cardiovascular in nature, such as walking and cycling.

No published information is currently available for other forms of exercise such as resistance training for the heart failure patient. However, there is increasing evidence that resistance training is beneficial for the elderly as well as many other cardiac patients (Brechue and Pollock, 1996; Frontera et al, 1988, Frontera & McCarther, 1990; Ghilarducci et al., 1989; Kelemen et al., 1986). Resistance training can increase overall strength, bone mineral density, cardiovascular endurance and psychological well-being (Brechue and Pollock, 1996; Fiaterone et al., 1990). Typically, patients with heart failure develop significant skeletal muscle atrophy which could be an important contributor to exercise intolerance (Magnusson et al., 1994; Mancini et al., 1992; Minotti et al., 1991). Therefore, the use of resistance training could potentially provide an important means to improve or maintain skeletal muscle strength and endurance. This improved function may result in a greater ability to perform activities of daily living. Current guidelines by the AHA and other organizations do not include recommendations for a resistance training component for heart failure patients. However, it would seem the use of light to

moderate resistance training should be integrated as part of a well-rounded program for the low risk (AHA: Class B) heart failure patient.

Thus, the principles of exercise prescription for heart failure patients are similar to those for healthy people (Pollock & Schmidt, 1995). The major differences relate to the application of these principles to the patient. The goal of an exercise program for the heart failure patient is to reduce morbidity associated with the disease and maintain functional capacity for independent living. Generally, heart failure patients should start out slowly, and initially aim to increase duration of exercise. How well the heart failure patient adapts to the training program should dictate the frequency and magnitude of progression.

Summary of Review of Literature

Heart failure develops as a response to an insult to the cardiovascular system. This insult results in a series of cardiac, circulatory, and muscular alterations with short- and long-time constants. These compensatory adaptations may initially be remarkably effective in normalizing cardiocirculatory function. Yet, the compensatory changes which are thought to be beneficial at rest appear to become restrictive during an acute bout of exercise. Furthermore, most compensatory changes exact a price and eventually give rise to many of the clinical manifestations of heart failure, including marked exercise intolerance and chronic fatigue.

As a result it is hypothesized that it is not until the compensatory mechanisms with long-time constants become less needed that exercise tolerance will improve in

patients with heart failure (Zelis et al., 1991). Zelis et al. (1991) propose the following treatment strategy aimed at the gradual reversal of those compensatory mechanisms with long time constants (1) venodilation, (2) renal vasodilatation and improvement in renal flow, (3) reduction in vasoconstrictor and fluid regulatory hormones, (4) diuresis and improvement in skeletal muscle vasodilator capacity, (5) increased physical activity, (6) further increased physical activity (i.e. exercise training), (7) conditioning-induced increased vasodilatory capacity, (8) conditioning-induced metabolic adaptations in skeletal muscle, (9) increased aerobic capacity, and (10) continued reinforcement of the cycle by retracing the steps of the process.

Thus, patients with medically stable heart failure should be considered for participation in an exercise training program. Guidelines for and components of an exercise program for the heart failure patient are similar to other clinical populations and healthy individuals. However, the exercise prescription should be designed to meet the unique goals and demands of the patient.

CHAPTER 3
METHODOLOGY

Patient Characteristics

Patients for this study were recruited from the Department of Medicine, Cardiology Section, University of Florida and the Veterans Administration Medical Center (VAMC), Gainesville, FL. All potential patients were diagnosed with heart failure (NYHA Classification II and III) secondary to left ventricular dysfunction (LVEF $\leq$ 40%). The etiology of heart failure in all patients was ischemic heart disease due to coronary artery disease, based on documented myocardial infarction and/or cardiac catheterization. The duration of heart failure was no less than 4 months. All patients were over the age of 18, and were on optimal heart failure pharmacotherapy including (1) digitalis glycosides, and/or (2) ACE-inhibitors, and/or (3) diuretics. Patients with unstable angina, uncontrolled hypertension and/or uncontrolled diabetes mellitus, significant chronic lung disease, signs of renal failure or recent myocardial infarction (less than 5 weeks) were excluded from participation in the study. Patients with cardiac pacemakers, internal defibrillators, and those with significant musculoskeletal problems that would interfere with their ability to engage in an exercise trial were also excluded from participation.

Thirty-four patients meeting these criteria volunteered to participate in the study and were scheduled for a screening visit. During this initial screening visit the entire protocol, the inherent risks and benefits of the study, and necessary time commitments were explained. Following this explanation written informed consent was obtained from each patient who wished to continue. All procedures outlined in the informed consent were approved by the University of Florida College of Medicine Institutional Review Board (Appendix A).

Experimental Protocol

Screening and Orientation

All potential subjects were recruited from the Department of Medicine, Cardiology Section, University of Florida and the VAMC, Gainesville, FL. Those patients who had no contraindications (see exclusion criteria) were asked to volunteer for the study. All patients received a comprehensive explanation of the proposed study, its benefits, inherent risks and expected commitments with regard to time. Following the explanation of the proposed study, all patients were allowed a period of questioning and further clarification.

Initial Testing (TI)

Visit 1 (Evaluation of exercise tolerance and capacity)

Those patients who were willing to participate were scheduled for an initial visit at the Center for Exercise Science, Florida Gymnasium. Upon arriving at the Center, the patient was asked to read and sign an informed consent document, complete dietary and quality of life questionnaires, receive a medical examination and undergo an SL-GXT.

After the informed consent was obtained, the subject was seated in a quiet room for 15 minutes whereafter resting heart rate and blood pressure were obtained using standard auscultation procedures and a Trimline mercury sphygmomanometer (Pymah Co., Somerville, NJ) Then, body composition was assessed anthropometrically from the sum of 7 skinfold fat sites (chest, axilla, triceps, subscapular, abdominal, suprailium, and thigh). All measurements were obtained from the right side of the body with a Lange skinfold fat caliper (Cambridge Scientific Industries, Cambridge, MD). The methods used for obtaining skinfolds and measures of body composition have been previously outlined by Pollock & Wilmore (1990).

Following this evaluation a medical examination was performed by qualified personnel and a 20 gauge polyethylene cannula was placed into an antecubital vein of the right arm. The medical examination included a general evaluation and assessment of cardiac function and clinical symptoms. Catheter placement was performed under aseptic conditions and kept open by filling the catheter with dilute heparinized saline.

Then each subject was prepared to undergo a walking SL-GXT to determine VO_{2peak}. The exercise protocol consisted of an SL-GXT using an incremental treadmill (Quinton Instruments, Seattle, WA) exercise protocol (Modified-Naughton) (Naughton, 1973). The initial workload on the treadmill was 2.0 mph at 0% grade and progressed every 2 minutes by increasing the grade by 2% until the subject reached voluntary maximal exertion or became symptomatic with positive hemodynamic or medical indices.

The following criteria recommended by the ACSM were used for termination of the SL-GXT (1):

1. Fatigue,

2. Failure of monitoring equipment,

3. Light-headedness, confusion, ataxia, cyanosis, dyspnea, nausea or any peripheral circulatory insufficiency,

4a. Onset of grade II/III angina pectoris (moderate to severe) with exercise,

b. Mild angina pectoris with 2 mm of ST segment depression,

5. Symptomatic supraventricular tachycardia,

6. "ST" segment displacement 4 mm or greater in the absence of angina pectoris,

7. Ventricular tachycardia (3 or more consecutive premature ventricular contractions (PVC)),

8. Exercise induced left bundle branch block,

9. Onset of second and/or third degree atrial-ventricular block,

10. R on T PVC's (one),

11. Frequent multifocal PVC's (30% of the complexes),

12. Excessive hypotension (greater then 20 mm Hg drop in systolic blood pressure during exercise),

13. Excessive blood pressure rise: systolic blood pressure greater or equal to 220 or diastolic blood pressure greater or equal to 110 mm Hg,

14. Inappropriate bradycardia: drop in heart rate greater than 10 beats.min^{-1} with an increase or no change in workload.

During the test, expired gases were collected through a low-resistance two-way valve (Hans Rudolph Inc., Kansas City, MO). Samples of the expired gases were analyzed using a metabolic cart (Medical Graphics Corporation, St. Paul, MN). The system was calibrated with standard gases of known concentrations before and after each test. Minute ventilation (VE) was determined by an electronic flow meter on the expired side of the circuit. Volume calibration was performed with a 3-liter calibration syringe. Analog outputs from each device was continuously monitored by an on line microcomputer via an analog-to-digital conversion board. This provided breath by breath determination of VO_2, VCO_2 and VE.

Heart rate, and 12 lead electrocardiogram (ECG) were monitored and recorded throughout the test using standard lead placement with a Quinton Q 4000 system (Quinton Instruments, Seattle, WA). Blood pressure measurements, ratings of perceived exertion (RPE), and symptoms of angina and/or dyspnea were also obtained at the end of each minute throughout the test using a standard sphygmomanometer, the 15 point Borg's perceived exertion scale, and the 4-point dyspnea and angina scales recommended by the ACSM, respectively (American College of Sports Medicine, 1995).

Two minutes prior to the start of exercise a qualified person obtained a 20 ml blood sample. The blood sample was drawn into a single plastic syringe and separated in individual aliquots for analyses of neuroendocrine hormones and metabolites (see below for details). To determine the response to acute exercise, an additional 20 ml blood sample was obtained immediately following termination of the exercise test. For the purpose of standardization all blood samples were obtained in the upright position.

Following the SL-GXT patients were allowed to recover for 30 min in a quiet room. During the recovery period, patients were asked to complete a quality of life questionnaire which included a series of questions designed to measure perceived health problems and the extent to which such problems affected their individual daily activities. Prior to discharge vital signs were once more obtained and if the patient was deemed suitable to continue in the study a follow-up visit was scheduled.

Visit 2 (Evaluation of cardiac function)

For day 2 of testing all subjects reported to the VAMC, non-invasive cardiology laboratory for the assessment of cardiac function using two-dimensional and Doppler echocardiography prior to, during and following an intermittent, incremental treadmill exercise test. To ensure adequate recovery Visit 1 and 2 were separated by a minimum of 72 hours but not more than 1 week. Two-dimensional and Doppler echocardiography were then performed using commercially available equipment (Hewlett Packard, Palo Alto, CA). Cardiac images were obtained with the transducer in the parasternal, and apical windows. Cardiac output was assessed by pulse-wave Doppler from the apical

window and continuous wave Doppler from the suprasternal notch. Prior to exercise, cardiac images and assessment of cardiac output were performed in both a supine and upright position.

The exercise protocol consisted of a three-stage exercise test on a motor driven treadmill. Each exercise stage lasted 4 minutes (or as symptoms permitted) and corresponded to 25%, 50%, and 75% of HR_{peak} determined during visit 1. During the last minute of each exercise stage blood flow velocities were determined using continuous wave Doppler from the suprasternal notch position. Immediately following each bout of exercise cardiac images were obtained in the upright position.

Throughout the test, simultaneous recordings for heart rate, and 12 lead ECG's were obtained at 1 min increments using standard lead placement and a Quinton Q-4000 system (Quinton Instruments, Seattle, WA). Blood pressure measurements, RPE's, and clinical symptoms were also obtained using a standard sphygmomanometer, Borg's RPE scale, and the scales recommended by ACSM (American College of Sports Medicine, 1995), respectively. The same criteria for termination of the SL-GXT during visit 1 were used during the second visit.

Visit 3 (Evaluation of skeletal muscle metabolism)

During day 3 of testing all subjects reported to the VAMC, Magnetic Resonance Imaging Laboratory for the assessment of skeletal muscle metabolism using ^{31}P NMR spectroscopy. Visits 2 and 3 were separated by a minimum of 48 hours but not more than 1 week, to allow for adequate recovery. Magnetic resonance imaging and nuclear

magnetic resonance spectroscopy were performed with a 1.5 tesla, 20 cm bore superconducting magnet (Signa GE Medical Systems, Milwaukee, WI), interfaced with a Fourier transform (FFT) spectrometer. Operating frequencies of 32.5 MHz were used for ^{31}P spectra. Each patient was positioned supine inside the magnet with a surface coil placed over the medial head of the gastrocnemius muscle and their foot attached to a non-ferromagnetic ergometer. The distance of the center of the surface coil on the medial gastrocnemius to the lateral epicondyle of the tibia was recorded for each patient to ensure accurate reproducibility on repeat tests. All measurements were obtained using the same leg.

Maximal voluntary contraction (MVC) was assessed using the right calf with the patient in a supine position in the magnet. Maximal voluntary contraction was determined in pounds per square inch (psi) for plantar flexion at full range of motion. The patient was verbally encouraged to maximize his or her effort.

Following the assessment of MVC, resting ^{31}P spectra were collected for a period of approximately 3 min, whereafter the patient performed a dynamic work test using repetitive plantar flexion at 25% of MVC for 10 minutes, or as tolerated. The rate of plantar flexion was one contraction every 4 seconds. Throughout the work bout and the ensuing 15 min recovery period continuous ^{31}P spectra were obtained.

After the 15 min recovery period, and prior to the start of the second dynamic work test another series of resting ^{31}P spectra were obtained. The rate of contractions for the second test were identical to the first. However, this time the patient exercised at 85%

of their MVC, to fatigue. Fatigue was defined as an inability to complete a contraction throughout the full range-of-motion. Following the exercise bout the recovery spectra were acquired for an additional 15 minutes.

Four-Week Evaluation (TII)

After one month patients were again scheduled to undergo the same series of experiments as described for TI. In order to control for the possible confounding effects of pharmacotherapy, circadian rhythms, and other external sources of variability the tests were performed by the same team of investigators at approximately the same time of day.

Following the second series of experiments, patients were randomly assigned to an exercise training (TR) or usual care group that did not train (NTR). Patients randomized to the usual care group were scheduled for weekly visits to monitor compliance, safety, and general physical condition.

Exercise Training Protocol

The TR group performed dynamic aerobic training on a treadmill at the Center for Exercise Science, under supervision by designated staff (exercise specialists and registered nurse). Each individual received appropriate instructions concerning warm-up and cool-down techniques, as well as how to monitor the intensity of exercise training by use of the RPE scale.

The training sessions were carried out three times per week for a total of 16 weeks. For the individuals participating in the TR group, each exercise training session consisted of either walking on the treadmill or stepping on a stair climber. The initial

exercise intensity was equivalent to 40-50% of the VO_{2peak} or maximal heart rate reserve (as determined by the treadmill SL-GXT) or as symptoms permitted. The intensity of the exercise sessions were gradually increased to 70-80% of VO_{2peak} towards the final 4 weeks of the exercise training period in those patients who exhibited appropriate exercise responses. The duration of each exercise session was initially 10 to 20 minutes or as tolerated and progressed to 40 to 60 minutes of sustained walking or stair climbing during the last 4 weeks of the study. An accurate log of the training parameters (heart rate, blood pressure, intensity, duration, RPE and treadmill/stair climber speed and grade) was kept for every training session for each individual. A "Crash-Cart" was available during all training sessions, in addition to individual supervision by staff trained in exercise prescription and cardiopulmonary resuscitation.

Twenty-Weeks Evaluation (TIII)

During the final evaluation period (TIII) all patients were again scheduled for the same series of experiments as determined for TI and TII.

Data Analysis

Echocardiography

Cardiac images were analyzed for left ventricular wall thickness, segmental left ventricular wall motion, ejection fraction, end-systolic and end-diastolic internal dimensions and volumes, stroke volume, and parameters of diastolic function. Doppler signals were obtained with the transducer in the suprasternal notch position. Prior to exercise and with the patient in a supine position, the diameter of the ascending aorta was

measured at the root. The aortic root dimension was defined as the distance between the leading edge of the anterior aortic wall and the leading edge of the posterior aortic wall at the R-wave of the ECG. It was assumed that the aortic root dimensions did not change from a supine to upright position, or rest to exercise transition. The area of the aortic root was determined using the equation: $A = 0.785d^2$, where A = area, and d = aortic root dimension. The Doppler signal was converted to a velocity measure using the following equations: (1) $f_d = f_r - f_t$, (2) $f_d = \{2f_t * [(v * \cos \Theta) / c]\}$, (2) $v = \{[f_d * c / 2f_t (\cos \Theta)]\}$, and (3) c = velocity of sound, where f_d = Doppler frequency, f_r = received frequency, f_t = transmitted frequency, v = integrated flow velocity, cos Θ = cosine of the angle theta, c = velocity of sound (approximately 1,540 meters per sec for soft tissue). Aortic flow was assumed to reflect cardiac output as this represents the volume of blood that perfuses the systemic circulation. Aortic flow measurements, or cardiac output, were determined from the equation: CO = A * V * HR, where CO = cardiac output, A = area of the aortic root, V = integrated flow velocity, and HR = heart rate.

^{31}Phosphorus-Nuclear Magnetic Resonance Spectroscopy

The spectra acquired from the above described experiments were analyzed using a SPARC/IPC work station and GE SA/GE software (Signa GE Medical Systems, Milwaukee, WI). Baseline corrections of the spectra were performed using standard procedures including (1) apodizing with 10 Hertz line broadening, and (2) the use of zero fill, FFT, phasing and sinc-deconvolution.

The relative concentrations of phosphomonoesters (PME), Pi, PCr, and the β-phosphate of adenosine 5'-triphosphate (ATP) were determined using the triangulation method assuming uniform distribution of the compounds throughout 670 cm^3 intracellular water.kg^{-1} wet weight of muscle (Arnold et al., 1984). It was also assumed that human muscle contains approximately 8.2 mmol ATP.kg^{-1} wet weight, and the total amount of creatine and PCr remained constant at 28.5 mmol.kg^{-1} wet weight of muscle (Arnold 1984) The equation used to determine concentrations was: Area of metabolite = [(Height of metabolite peak * baselength of metabolite peak) / 2]. Concentrations were divided by the average area of beta ATP at rest to correct for noise and then multiplied by the relaxation time for the metabolite to correct the calculated concentration ratios for differences in saturation. The relaxation time for each metabolite for this laboratory had been previously established by Dr. Ballinger (Ballinger, 1994) and included (1) PME = 0.92, (2) Pi = 0.95, (3) PCr = 0.92. The general equation to determine the concentrations of PME, Pi, and PCr is listed below:

[Metabolite] = (Area * Relaxation time * 8.2 mM of ATP) / Average area of beta ATP at rest.

Intracellular pH was determined from the chemical shift difference between Pi and PCr. Using the chemical shift intracellular pH was calculated as $6.75 + \log(\sigma - 3.27)/(5.69 - \sigma)$, where σ is the peak position of Pi referenced to PCr, in parts per million.

The cytosolic free concentration of adenosine diphosphate (ADP) was calculated from the PCr/ATP ratio and pH, using the equilibrium constant for the creatine kinase

reaction. Thus, the equilibrium equation for calculating the ADP was ADP = {(Average ATP_{rest} * 28.5) / (Keq) * 10-pH) * [PCr]}, where Keq is assumed to be 1.66 * 10^9 (Arnold, 1984).

The cytosolic concentration of diprotonated Pi ($H_2PO_4^-$) was also calculated assuming the pK for $H_2PO_4^-$ to be 6.75. The percentage of Pi in the diprotonated form was calculated as $H_2PO_4^-$= {(1 + $10^{(pH - 6.75)}$) * Pi}.

Analysis of PCr_{res} following exercise were performed by plotting the PCr peak areas acquired during the post-contraction phase against time and fitted to a monoexponential curve. The rate constant for each recovery test was determined by use of the following equation: $PCr = PCr_{ee} + (PCr_{ee} - PCr_f)(1 - (e^{(-k(t+c))}))$, where PCr_{ee}, is the end-exercise PCr, PCr_f is the final PCr, t is time, k is the rate constant, and c is a correction factor to optimize the curve fit and the natural log of 2 / k is the half time of recovery. The PCr_{res} was calculated from the equation $PCr_{rate} = k[PCr_0]$, where k is the rate constant (min^{-1}) and $[PCr_0]$ is the resting level of PCr ($mmol.kg^{-1}$). The PCr_{ee} was estimated using an average of the PCr during the last 3 exercise spectra.

Half times for recovery of ATP/ADP*Pi were calculated as half the number of spectra from the last exercise spectra to the spectra whose ratio equals or exceeds averaging resting values. This value was multiplied by 32 sec to get a half time.

Quality of Life Questionnaire: The Nottingham Health Profile

The Nottingham Health Profile was designed to measure perceived health problems and the extent to which such problems affect daily activities. However, it is

best to regard it as a measure of distress in the physical, emotional and social domain. The Nottingham Health Profile was tested for face, content and criterion validity in a series of studies carried out between 1978 and 1981. Testing of validity and reliability have taken place with the following groups (1) healthy elderly over the age of 65 (Hunt et al., 1981), (2) patients with a variety of disease states including (O'Brien et al., 1988): a) peripheral vascular disease, and b) osteoarthritis, and (3) a variety of individuals from all levels of the work force representing the age range from 19 to 75 years (Hunt et al., 1981). These studies have confirmed the questionnaire is suitable for use with a wide range of people, and demonstrates the consistency of responses to be satisfactory over time.

The questionnaire includes a series of statements which vary in the severity of the experiences they describe. For this reason each statement have been weighted using a method known as Thurstone's Method of Paired Comparisons. The use of the weighting system allows for a comparison over time, which is often necessary in longitudinal studies. The questionnaire provides a profile of perceived distress in the area of pain, physical mobility, emotional reactions, social isolation, sleep and energy.

Blood Samples

Hematocrit and hemoglobin

Blood samples were analyzed for hematocrit, hemoglobin, and plasma protein. Whole blood hematocrit was measured in triplicate with a microhematocrit centrifuge and a microcapillary tube reader (IEC, Model MB, Nedham Heights, MA). Hematocrit was

corrected for trapped plasma and for whole body hematocrit. Hemoglobin was also measure in triplicate using the cyanmethemoglobin method (Sigma Diagnostics, St. Louis, MO). Mean corpuscular hemoglobin was obtained by dividing the hemoglobin by the hematocrit. For the determination of plasma protein, 2 ml of whole blood were centrifuged at 3500 revolutions per minute for 15 min at 2-4° C and plasma was separated. Plasma proteins were analyzed in triplicate using a standard protein kit (Sigma Diagnostics, St. Louis, MO). The total protein content was calculated as the product of the plasma protein and plasma volume.

Calculation of blood volume, red cell volume and plasma volume

The relative changes in blood volume, red cell volume, and plasma volume were calculated according to the equations by Dill & Costill (1974). The blood volume at peak exercise was calculated based on changes in pre and peak exercise hemoglobin (Hb) and with the pre-exercise blood volume based on a relative volume of 100 ml [blood $volume_{peak}$ = blood $volume_{pre}$ (Hb_{pre} / Hb_{peak})]. Change in blood volume was calculated as: blood volume (%) = 100 (blood $volume_{peak}$ - blood $volume_{pre}$) / blood $volume_{pre}$. Hematocrit determined prior to exercise was defined as cell $volume_{pre}$. Cell $volume_{peak}$ was calculated from blood $volume_{peak}$ and $hematocrit_{peak}$ (cell $volume_{peak}$ = blood $volume_{peak}$ * $hematocrit_{peak}$). The change in cell volume was calculated as: cell volume (%) = 100 (cell $volume_{peak}$ - cell $volume_{pre}$) / cell $volume_{pre}$. The plasma $volume_{pre}$ and plasma $volume_{peak}$ were calculated by subtracting the cell volume from the blood volume as determined above. The change in plasma volume with exercise was subsequently

calculated using: plasma volume(%) = 100 (plasma $volume_{peak}$ - plasma $volume_{pre}$) / plasma $volume_{pre}$.

Atrial natriuretic peptide radioimmunoassay

Atrial natriuretic peptide was extracted from thawed plasma samples using SepPak C18 (octadecyl silica) cartridges which were wetted and prewashed with 5 ml methanol, 1% trifluoroacetic acid (TFA), 1% polypep solution, 5 ml methanol/H_2O/TFA (80:19:1) and 5 ml 1% TFA. The samples were acidified with an equal volume of 1% TFA and applied to the cartridges. The cartridges were subsequently washed with 5 ml 1% TFA/1% NaCL, and the ANP was eluted with 3 ml methanol/H_2O/TFA (80:19:1), and dried under air at 35° C.

The radioimmunoassay commenced with the reconstitution of the atrial natriuretic peptide samples. This involved diluting and dissolving the samples, standards, antibody and ^{125}I-labeled ANP (rat) with a 0.1 M phosphate buffer with 0.05 NaCL, 0.1% bovine serum albumin, 0.1% Triton X-100 and 0.01% NaN_3. Antibody was added to the standard or samples and incubated for an additional 24 hours at 4° C. Bound atrial natriuretic peptide was precipitated with goat-anti-rabbit antiserum and normal rabbit serum by a 2 hour incubation. Samples were centrifuged at 2,000 g for 30 minutes at 4° C. The supernatant was discarded and the precipitate counted in a gamma counter (model 5500, Beckman). Counts per minute were fed directly into a data reduction system (DP550 Beckman), for logit-log method of analysis. This program calculates the best fit straight line by use of the linear regression statistical method.

Arginine vasopressin radioimmunoassay

Plasma arginine vasopressin was measured by radioimmunoassay using a rabbit anti-arginine vasopressin antibody. The anti-arginine vasopressin serum was generated in the laboratory of Dr. C. Wood, Department of Physiology, University of Florida. The anti-arginine vasopressin serum was generated using arginine vasopressin (Sigma Chemical) covalently linked to bovine thyroglobulin with carbodiimide. The crossreactivity of the antiserum with lysine vasopressin was 0.7%. Crossreactivity with oxytocin, vasotocin, arginine vasopressin (fragment 4-9), CRF, ACTH, angiotensin I, and angiotensin II was each <0.001%. Arginine vasopressin was extracted from plasma by adsorption to bentonite. Plasma (1.0 ml) was extracted and then reconstituted to 0.25 ml with assay buffer (0.05 M phosphate buffer, pH=7.4 containing 0.01 M EDTA and 0.2% BSA). 125I-arginine vasopressin (Dupont C., Wilmington, DE.) was used as tracer. The range of the standard curve was from 0.05 to 10 pg per tube. In previous studies using this assay, the intraassay coefficient of variation (CV) for a low pool (0.40 pg per tube) was 4% and for a high pool (4.0 pg per tube) was 14%. Interassay CV was 7% (0.35 pg per tube).

Angiotensin II radioimmunoassay

Plasma angiotensin II was measured using the radioimmunoassay technique after extraction on bentonite. This assay has been described in detail previously (Raff et al., 1985). The antiserum used has less than 1.0% cross-reactivity with angiotensin I and was

generated in the laboratory of Dr. C. Wood (Department of Physiology, University of Florida).

Aldosterone radioimmunoassay

Plasma aldosterone concentration was measured using the radioimmunoassay technique in unextracted serum using a kit available through Diagnostics Products Corp., Los Angeles, CA. Serum samples (0.2 ml) were added to polypropylene tubes coated with antibodies to aldosterone. Approximately 1 ml of ^{125}I aldosterone tracer was added to the tubes and after 3 hour incubation at 37°C the supernatant was decanted and the tubes counted on a gamma counter. Aldosterone concentration was determined from a standard curve. Intraassay CV for this procedure is 2.7-8.3% and interassay CV is 3.6-10.4%. The detection limit is approximately 16 $pg \cdot ml^{-1}$.

Statistical Analysis

All data are summarized as mean $\pm$ standard deviation. All data were analyzed for within and between group comparisons using analysis of variance for repeated measures. If a significant difference was detected, mean values were compared with a Newman-Keuls post-hoc test (Glantz, 1981). An alpha level of $p \leq 0.05$ was required for statistical significance. To determine the relationships among ^{31}P NMR spectroscopy, exercise capacity, neurohormones and measurements of cardiac function, pearson product-moment correlation coefficients were calculated. All statistical analysis were completed using the STATISTICA software statistical program (StatSoft Inc., Tulsa, OK).

Statistical analysis of the Nottingham Health Profile included the use of non-parametric statistics. For comparison of the trained and non-trained groups data were analyzed using a Mann-Whitney U-test. For analysis of repeated measures within the same group the Friedman two-way analysis of variance was performed. Statistical significance was accepted at p-values less than or equal to 0.05.

CHAPTER 4
RESULTS

The Acute Exercise Response in Heart Failure

Subject Characteristics

The baseline characteristics of the 34 patients who participated in the study to evaluate the acute responses to a single bout of exercise are presented in Table 4.1. The mean age, height, and weight for the heart failure patients (HF) was 61±6 yrs, 176±14 cm, and 96±30 kg, respectively. The average percent body fat for HF was 27.35±7.40%, with an estimated fat weight of 27.73±14.58 kg and lean body mass of 62.60±7.0 kg. The average duration of HF was 5±3 yrs, and the mean LVEF was 29.50±6.73%. The etiology of HF was ischemic heart disease in all patients and the average value for the NYHA classification was 2.5±0.49.

To compare the acute exercise responses during symptom-limited graded exercise and the ^{31}P-NMR spectroscopy protocol, a healthy age-matched control (CON) group was selected to match the HF group as closely as possible. The CON subjects were normally active individuals who had no evidence of underlying disease as determined by previous clinical examination. The mean age, height, and weight for the CON subjects was 63±6 yrs, 181±12 cm, and 91±26 kg, respectively. The average percent body fat was 25.12 ± 5.62%, with an estimated fat weight of 22.15±9.90 kg.

Evaluation of Exercise Capacity

The mean values for the cardiopulmonary variables obtained during the SL-GXT are summarized in Table 4.2. The average pre-exercise VO_2 (VO_{2prex}) was 299±83 $ml.min^{-1}$ (3.11±0.78 $ml.kg^{-1}.min^{-1}$) and changed nearly 4-fold at peak exercise (VO_{2peak}) to 1139 $ml.min^{-1}$ (12.15±3.48 $ml.kg^{-1}.min^{-1}$). This VO_{2peak} of 1139 $ml.min^{-1}$ is approximately 62% of the VO_{2peak} observed in the CON, indicating marked exercise intolerance. The average pre-exercise VE (VE_{prex}) was 13.09±4.0 and increased 243% to 45.41±9.97 $L.min^{-1}$ at peak exercise ($p \leq 0.05$). Peak ventilatory equivalent for VO_2 (VE/VO_{2peak}) was 39.87±3.23 at peak exercise. The VE/VO_{2peak} in HF was markedly higher than for CON indicating a greater need for VE for a given O_2 uptake.

Exercise Tolerance and Time

Ratings of perceived exertion and clinical symptoms and peak exercise time achieved during the SL-GXT are summarized in Table 4.3 for HF and CON. The mean values for HF for RPE, angina, and dyspnea at peak exercise were 16±3 (n=32), 2.5±1 (n=9), and 3.0±1 (n=28), respectively. The mean exercise time on the modified Naughton exercise protocol was 8.4±3.5 min, achieved at a work load of 2 mph and 6% grade. In contrast the mean RPE value for CON was 18±2, whereas the mean exercise time was 16.2±3.8min and significantly greater versus HF.

Cardiac Responses to an Acute Bout of Exercise

The mean values for the cardiovascular variables obtained during the SL-GXT are summarized in Table 4.2. The average pre-exercise heart rate (HR_{prex}) for HF was 73±16

beats.min^{-1} and increased 78% to 125±18 beats.min^{-1} at HR_{peak} ($p \leq 0.05$). The mean chronotropic reserve was 54±8 beats. The rate pressure product ([beats.min^{-1} * systolic blood pressure]/100), an indicator of myocardial O_2 demand, was estimated at 207±40 at peak exercise. The pre-exercise O_2pulse (O_2pulse_{prex}) was 4.37±1.26 ml.beat^{-1} and increased 119% to 9.58±2.14 ml.beat^{-1}. Mean values for CON indicated a greater reserve capacity as evidenced by an 82±9 beat chronotropic reserve, a 272% increase in O_2pulse and much larger rate pressure product at peak exercise

The mean cardiac responses to submaximal exercise in HF are presented in Table 4.4 and Figure 4.1. The average supine stroke volume was estimated at 79±20 ml. There was a 37% decrease in estimated stroke volume in the upright, pre-exercise position (49±22 ml) compared to the supine position ($p \leq 0.05$). The average stroke volume increased 46%, to 72±28 ml, compared to standing values, at a workload calculated to elicit 25% of the HR_{peak} observed during the SL-GXT. At 50% of the patient's HR_{peak} the mean stroke volume (65±27 ml) was still significantly higher compared to the standing pre-exercise values, yet slightly less than the stroke volume observed at 25% of the HR_{peak}. At 75% of HR_{peak} a further decline in stroke volume was noted (62±23 ml). Although the decline was not statistically significant, the percent decrease was 5.3% and 14% compared to the stroke volumes observed at 50% and 25% of HR_{peak}, respectively.

The estimated mean supine cardiac output was estimated at 6.54±1.93 L.min^{-1}. Upon standing there was a 33% decrease in cardiac output (4.35±1.67 l.min^{-1}) compared to the supine position ($p \leq 0.05$). The average cardiac output at 25% of HR_{peak} increased

46%, to 6.41±2.80 $L.min^{-1}$, compared to the pre-exercise standing values. At 50% of the patient's HR_{peak} a small increase in the average cardiac output (7.00±2.72 $L.min^{-1}$) was noted. However, the 8.8% increase was not statistically different from those observed at 25% of HR_{peak}. At 75% of HR_{peak} a further increase in the mean cardiac output was noted (7.52±2.93 $L.min^{-1}$). The cardiac output at 75% was 7.3% and 16% larger, compared to the values observed at 50% and 25% of HR_{peak}, respectively. Thus, it appears that the increase in cardiac output is mediated by both an increase in stroke volume and heart rate at 25% of HR_{peak}. However, at 50% and 75% of HR_{peak} the increase in cardiac output was, solely dependent on the increase in heart rate, since stroke volume declined.

Circulatory Responses to an Acute Bout of Exercise

The mean values for the circulatory responses obtained during the SL-GXT are summarized in Table 4.2.

Blood pressure responses to acute exercise

The mean pre-exercise systolic (SBP_{prex}) and diastolic (DBP_{prex}) blood pressure was 126±17 over 76±8 mmHg and increased significantly with exercise, to 166±15 over 88±9 mmHg ($p \leq 0.05$). In addition, the mean arterial pressure (MAP) increased from 93±9 mmHg at rest to 114±10 mmHg at peak exercise ($p \leq 0.05$). In the CON group there was no significant difference in SBP_{prex} (120±17 mm Hg), DBP_{prex} (76±8 mmHg) or MAP_{prex} (87±8 mmHg) compared to the HF group. However, SBP at peak exercise (SBP_{peak}) (191±17 mmHg) was significantly higher in the CON group.

Relative changes in blood volume, cell volume, and plasma volume during acute exercise

Exercise was associated with a significant change in hemoconcentration, as presented in Table 4.5. Hematocrit, Hb, and plasma protein concentration increased with corresponding decreases in plasma volume and blood volume. The average pre and peak exercise hematocrit (corrected) and Hb were 39.40±3.92% and 40.9±3.48%, and 16.77±3.48 and 18.48±4.53 $g.dl^{-1}$ ($p \leq 0.05$), respectively. These values indicated a 3.8% increase in hematocrit and an 8.9% increase in Hb from pre to peak exercise and a corresponding 8.4±5.21% decrease in blood volume and 10.55±5.22% decrease in plasma volume ($p \leq 0.05$) suggesting a fluid efflux from the vascular compartment (Figure 4.2). The exercise induced hemoconcentration remained significantly elevated until 20 min in recovery.

Plasma protein concentration increased from pre to peak exercise (7.11±1.26 to 7.61±1.20 $g.dl^{-1}$), indicating an 7.3% increase ($p \leq 0.05$), however, total protein content did not change. Mean corpuscular hemoglobin concentration obtained by dividing Hb by hematocrit was 43.19±2.10 pre-exercise and 45.40±1.90 at peak exercise indicating a 4.9% increase ($p \leq 0.05$).

Humoral responses to acute exercise

Measurements of plasma angiotensin II, arginine vasopressin, aldosterone, and α-atrial natriuretic peptide were obtained before and immediately after exercise in the standing position. Based on the relative changes in blood volume and plasma volume, the peak exercise neurohumoral concentrations were corrected for a 10.6% decrease in

plasma volume. Pre-exercise and peak exercise concentrations of the neuroendocrine hormones during the SL-GXT, for HF are presented in Table 4.6.

Angiotensin-aldosterone response to acute exercise. Pre-exercise plasma angiotensin II and aldosterone were 5.2±1.2 pg•ml^{-1} and 152±31 pg•ml^{-1}, respectively. Pre-exercise values are approximately 92% and 27% higher than those observed in a healthy group previously studied in this laboratory using similar standardization and assay procedures (Braith et al., 1991). After correction of plasma volume shifts, the peak exercise angiotensin II increased 175% to 14.3±1.9 pg•ml^{-1} ($p \leq 0.05$ vs. pre-exercise), whereas the peak aldosterone was not significantly different from pre-exercise values, 169.1±52 pg•ml^{-1}.

Arginine vasopressin response to acute exercise. Pre-exercise plasma arginine vasopressin was 6.0±1.6 pg•ml^{-1}. These values are approximately 114% higher than those previously observed in healthy volunteers studied in this laboratory (Braith et al., 1991). After correction of plasma volume shifts, the peak exercise arginine vasopressin increased 163% to 15.8±3.7 pg•ml^{-1}, which was significantly different from pre-exercise values ($p \leq 0.05$).

Atrial natriuretic peptide response to acute exercise. Pre-exercise plasma atrial natriuretic peptide was 36.0±9.0 pg•ml^{-1}. These values are approximately 98% higher than those observed in a healthy control group studied in this laboratory by Dr. Braith (Braith et al., 1991). After correction of plasma volume shifts, the peak exercise atrial

natriuretic peptide increased 60% to 57.6±13.7 $pg \cdot ml^{-1}$ which was significantly different from pre-exercise values ($p \leq 0.05$).

Skeletal Muscle Response to an Acute Exercise Bout

Skeletal muscle strength, circumference and endurance

The mean values for MVC, calf circumference, and exercise time for HF and CON are presented in Table 4.7. Maximum voluntary contraction, as assessed by plantar flexion exercise, was similar between the HF and CON (HF: 86±21; CON: 93±24 psi). The average calf muscle circumference for HF was 36±5 cm versus 35±5 cm in the CON group. Exercise time for the low intensity (25% MVC) in-magnet work bout was 600 sec for all subjects. However, the mean exercise time for the high intensity (85% MVC) in-magnet work bout was significantly less for HF compared to CON (HF: 253±20; CON: 405±30 sec) ($p \leq 0.05$).

Skeletal muscle metabolic responses to acute exercise

Pi and PCr response to acute exercise (low intensity). The Pi and PCr responses to low intensity exercise are shown in Table 4.8 and the Pi/PCr ratio illustrated in Figure 4.3. The mean values for Pi (HF: 4.89±1.22; CON: 4.58±1.54 mM) and PCr (HF: 39.05±3.82; CON: 38.71±3.14 mM) were similar for both groups prior to exercise. With the onset of exercise there was a marked and rapid increase in Pi and a concomitant decrease in PCr for both groups, which was significantly different from pre-exercise ($p \leq 0.05$). In both groups the Pi and PCr reached a plateau after approximately 120 sec into the work bout. The mean end exercise values for Pi (HF: 12.98±2.41; CON:

8.89±1.95 mM) and PCr (HF: 19.15±3.92; CON: 28.81±2.99 mM) were statistically different from pre-exercise and between groups ($p \leq 0.05$). The percent depletion and increase in PCr and Pi, for the HF and CON groups during the low intensity exercise bout, was 43.40±4.62% and 25.09±3.80%, and 144±9.00% and 95±7.00%, respectively. Thus, the magnitude of change was significantly greater in HF compared to CON.

The pre-exercise Pi/PCr ratio (Pi/PCr_{prex}) was similar between HF and CON (HF: 0.13±0.04; CON: 0.12±0.03). With the onset of exercise the Pi/PCr ratio increased rapidly and reached a plateau after approximately 120 sec into the work bout. Both groups remained at this plateau for approximately 440 sec, until the end of the exercise bout. However, although, the exercise time was not different between groups, the average end exercise Pi/PCr ratio (Pi/PCr_{ee}) was significantly different between groups, with HF demonstrating a much higher Pi/PCr_{ee} compared to CON (HF: 0.67±0.10; CON: 0.31±0.08) ($p \leq 0.05$).

The PCr recovery curves were fitted by a single exponential. An example of the PCr recovery curves following exercise in a HF subject and healthy CON are illustrated in Figure 4.4. Based on the PCr recovery slopes, the PCr_{res} was determined. The half times (T1/2) for PCr_{res} are also presented in Table 4.8. The PCr_{res} (T1/2) were significantly greater in HF, ranging from 37.5 to 99.0 sec, and a mean of 62.0±27.0 sec, versus 14.5 to 43.0 sec and a mean of 26.5±13.0 sec for CON ($p \leq 0.05$). In addition, as presented in Figure 4.5, the relationship between the level of PCr depletion and resynthesis was described by the slope 0.00030 for the HF group, whereas the slope for

the CON group was 0.00213. This indicates that PCr recovery is independent of the level of depletion in HF.

Intramuscular pH response to exercise (low intensity). The mean intramuscular pH response to low intensity exercise is shown in Table 4.8 and Figure 4.6. The average pre-exercise intramuscular calf muscle pH (pH_{prex}) was similar for both groups (HF:7.09±0.04; CON: 7.10±0.04). With the onset of exercise there was a slight, but statistically significant increase in pH from pre-exercise values ($p \leq 0.05$) (see Figure 4.6). This brief alkaline shift lasted approximately 90 sec and was followed by a gradual but steady decline in pH for both groups. The pH decline during exercise was more marked in the HF group and the end exercise pH (pH_{endex}) was statistically different between groups (HF:6.99±0.10; CON: 7.10±0.07) ($p \leq 0.05$).

Immediately following exercise a marked drop in muscle pH was observed in both groups. The average post exercise low (pH_{trough}) occurred at approximately 120±35 sec in recovery for HF and at 90±32 sec for the CON group (HF: 6.89±0.14; CON: 7.01±0.08). The pH_{trough} was significantly different from pH_{prex}, pH_{endex}, and between groups ($p \leq 0.05$). The pH_{trough} was followed by a gradual return to pre-exercise values during the remaining 12 to 13 min of recovery. Statistical interpretation of the recovery slopes for pH were hampered by measurement variability and are therefore not reported.

H_2PO_4 changes during acute exercise (low intensity). The mean $H_2PO_4^-$ response to low intensity exercise is shown in Table 4.8 and Figure 4.7. Mean pre-exercise values for $H_2PO_4^-$ (HF: 1.54±0.19; CON: 1.53±0.23 mM) were similar for both groups. With

the onset of exercise there was a gradual increase in $H_2PO_4^-$ in both groups. In the CON group, the $H_2PO_4^-$ reached a plateau after approximately 120 sec into the work bout. In contrast, in HF $H_2PO_4^-$ continued to rise before reaching a plateau at approximately 300 sec into the work bout. The changes in $H_2PO_4^-$ with exercise were significantly different from pre-exercise values. End exercise values for $H_2PO_4^-$ (HF: 4.65±1.32; CON: 2.66±1.08 mM) were also statistically different from pre-exercise and between groups ($p \leq 0.05$). The percent increase in $H_2PO_4^-$, during low intensity exercise, was 201±32%, and 76±22%, for the HF and CON subjects, respectively.

ATP/ADP*Pi changes during and following acute exercise (low intensity). The ATP/ADP*Pi ratio changes with low intensity exercise are shown in Table 4.8 and illustrated in Figure 4.8. Prior to exercise, the mean values for ATP/ADP*Pi were similar between groups (HF: 40.46±6.22; CON: 42.58±5.54). The pattern of ATP/ADP*Pi with exercise was similar but in the opposite direction from the Pi/PCr curves described above. With the onset of exercise the ATP/ADP*Pi ratio declined rapidly reaching a steady state after approximately 120 sec. As for the Pi/PCr ratio there was a slight return toward pre-exercise values during the last minute of exercise in some patients. The mean end exercise values for ATP/ADP*Pi (HF: 9.58±1.61; CON: 11.89±1.95) were statistically different from pre-exercise but similar between groups ($p \leq 0.05$).

The ATP/ADP*Pi recovery half times, for HF and CON, are presented in Table 4.8. The mean values for the ATP/ADP*Pi recovery slopes following exercise in the HF subjects and healthy CON are illustrated in Figure 4.9. The recovery slopes for

ATP/ADP*Pi were remarkable for a rapid linear rise toward baseline during the first 90 to 100 sec in recovery and a subsequent "overshoot" of the ATP/ADP*Pi signal above the pre-exercise values lasting approximately 360 to 420 sec. The average ATP/ADP*Pi half times were significantly greater in the patients with HF compared to the CON group (HF: 64 $\pm$ 21; CON: 31 $\pm$ 10 sec) ($p \leq 0.05$).

Ratings of perceived exertion during acute exercise (low intensity). The mean end exercise RPE for both groups is shown in Table 4.7. The mean end exercise RPE was significantly higher for the HF subjects compared to CON (HF: 15$\pm$2.5; CON: 11$\pm$3.0) ($p \leq 0.05$). An average rating of 15 on the 16-grade scale indicated that the HF patients perceived the low intensity work load as *"Hard"*. A rating of 11, as reported for the CON group, indicated that the work was perceived as *"Fairly Light"*.

Pi and PCr response to acute exercise (high intensity). The average Pi and PCr responses to high intensity exercise are shown in Table 4.9 and the Pi/PCr ratio depicted in Figure 4.10. The mean pre-exercise values for Pi (HF: 4.59$\pm$1.02; CON: 4.68$\pm$1.76 mM) and PCr (HF: 38.55$\pm$4.12; CON: 36.31$\pm$4.02 mM) were similar for both groups and to pre-exercise values prior to the low intensity workload. As observed during the low intensity exercise, there was a marked and rapid increase in Pi and a concomitant decrease in PCr at the onset of exercise for both groups. The mean end exercise values for PCr (HF: 13.11$\pm$4.00; CON: 13.81$\pm$3.99 mM) were statistically different from pre-exercise and the low intensity end exercise values ($p \leq 0.05$), yet similar between groups. In contrast, the mean end exercise values for Pi (HF: 17.98$\pm$3.31; CON: 13.86$\pm$1.75 mM)

were significantly greater in heart failure ($p \leq 0.05$). The percent depletion in PCr was similar between groups (~64 %), but significantly greater compared to low intensity exercise ($p \leq 0.05$). The percent increase in Pi was significantly different between groups with a 292±14% increase in the HF patients compared to 196±12% for CON.

As observed during low intensity exercise the Pi/PCr_{prex} was similar between HF patients and CON (HF: 0.11±0.03; CON: 0.12±0.03). With the onset of exercise the Pi/PCr ratio again rose rapidly in both groups. The mean Pi/PCr_{ec} was significantly different from Pi/PCr_{prex} ($p \leq 0.05$). Furthermore, there was a significant difference between groups, with the HF patients demonstrating a much higher Pi/PCr_{ec} (HF: 1.56±0.36; CON: 1.00±0.19).

The PCr_{res} (T1/2) following the high intensity exercise bout are presented in Table 4.9. The half times were similar to those observed during the low intensity trial. The PCr_{res} (T1/2) for patients with HF ranged from 43.5 to 138.0 sec, with a mean of 68.5±24.0 sec, versus 14.5 to 43.0 sec with a mean of 29.5±13.0 sec for the age-matched CON ($p \leq 0.05$). Furthermore, as shown in Figure 4.5, the relationship between the level of PCr depletion and recovery was described by the slope 0.00005 for HF, whereas the slope for the CON group was 0.00042. This confirms the data observed during low intensity work which suggests that recovery is independent of the level of depletion in the HF group.

Intramuscular pH response to acute exercise (high intensity). The average intramuscular pH response to high intensity exercise is shown in Table 4.9. The mean

calf muscle pH was similar for both groups at rest (HF:7.08±0.04; CON: 7.11±0.01). With the onset of exercise there was a slight, but statistically significant increase in pH from pre-exercise values ($p \leq 0.05$). This brief alkaline pattern lasted approximately 90sec and was followed by a gradual but steady decline in pH for both groups. Although, the mean end exercise pH were significantly different from the end exercise values observed during the low intensity work bout, there was no statistical difference between groups (HF:6.85±0.09; CON: 6.89±0.06).

The average pH_{trough} occurred at approximately 120±35 sec and 80±32 sec in recovery for HF and CON subjects, respectively (HF: 6.59±0.13; CON: 6.62±0.09). The pH_{trough} was significantly different from pre and end exercise pH values ($p \leq 0.05$). The pH_{trough} in muscle pH was followed by a gradual return to pre-exercise values during the remaining 12 to 13 min of recovery.

$H_2PO_4^-$ changes during acute exercise (high intensity). The average $H_2PO_4^-$ response to high intensity exercise is shown in Table 4.9 and Figure 4.11. The mean pre-exercise values for $H_2PO_4^-$ (HF: 1.43±0.25; CON: 1.63±0.21mM) were similar for both groups and to the low-intensity workload. The mean end exercise $H_2PO_4^-$ was approximately double for both groups compared to the end exercise values for the low intensity workload. The mean end exercise values for $H_2PO_4^-$ (HF: 8.46±2.10; CON: 5.76±1.48 mM) were statistically different from pre-exercise, the low intensity end exercise values, and between groups ($p \leq 0.05$). The percent increase in $H_2PO_4^-$, during

high intensity exercise, was 512±145%, and 299±102%, for the HF and CON groups, respectively.

ATP/ADP*Pi changes during and following acute exercise (high intensity). The ATP/ADP*Pi ratio changes with high intensity exercise are shown in Table 4.9 and illustrated in Figure 4.12. Prior to exercise, the mean values for ATP/ADP*Pi were similar to low intensity and between groups (HF: 40.46±6.22; CON: 44.58±5.54). With the onset of exercise there was a marked and rapid decline in ATP/ADP*Pi in both groups. The mean end exercise values for ATP/ADP*Pi (HF: 8.53±2.01; CON: 7.18±1.95) were statistically different from pre-exercise but similar between groups ($p \leq 0.05$). The ATP/ADP*Pi (T1/2) are presented in Table 4.9. The pattern of the recovery slopes for ATP/ADP*Pi was similar to that observed during low intensity exercise. This includes the "overshoot", which lasted approximately 380 sec in both groups. However, the average ATP/ADP*Pi (T1/2) were significantly greater in the patients with HF compared to the CON group (HF: 51±19; CON: 21±8 sec) ($p \leq 0.05$).

Ratings of perceived exertion during acute exercise (high intensity). The mean end exercise RPE values for the high intensity workload were similar for both groups, suggesting all subjects reached a similar level of volitional fatigue (HF: 18±2.5; CON: 18±2.0). The average rating of 18 on the 15-grade scale indicates that the subjects perceived the high-intensity workload as near *"Very, Very Hard"*.

Adenosine triphoshate (ATP) during low and high intensity exercise. Mean values for ATP prior to exercise, presented in Table 4.7 and Table 4.9, were similar for

both groups (HF:8.16±0.97; CON:8.45±0.87 mM). With exercise there was a slight decrease in the mean ATP in both groups but this did not reach statistical significance.

The Response to Exercise Training in Heart Failure Patients

Patient Characteristics

Four of the 32 patients randomized to the training (TR) or non-training (NTR) group did not complete the 16 week trial and were therefore eliminated from final analyses. Two of the 4 subjects who did not complete the study were randomized to TR. One subject was forced to stop because of a worsening medical condition, whereas the second subject was terminated for poor compliance. The 2 subjects who were randomized to NTR were also dropped from the study due to poor compliance. Descriptive data for the remaining subjects are presented in Table 4.10. The mean values for age (TR: 61±7; NTR: 62±8 yrs), height (TR: 172±16; NTR: 178±14 cm), weight (TR: 96±29; NTR: 94±31 kg), percent body fat (TR: 28±6; NTR:27±7%) and LVEF (TR: 30±6; NTR: 29±7%), and NYHA classification (TR: 2.38±0.5; NTR: 2.50±0.5) were not significantly different between groups. Seven subjects in the non-exercise group and 8 subjects in the exercise group were status post coronary artery bypass. Twelve subjects in the non-exercise group, and 13 subjects in the exercise group were status post myocardial infarction. Four subjects in the non-exercise, and 3 subjects in the exercise group received treatment for diabetes mellitus. Seven subjects in the non-exercise, and 5 subjects in the exercise group were treated for hypertension. All patients were on standard heart failure pharmacotherapy, which included (1) digitalis glycosides, (2) ACE-

inhibitors, and (3) diuretics. Additional pharmacotherapy, such as beta-blockers, anticoagulants, antihyperlipidemics, and antihypertensives were equally distributed between groups.

Evaluation of Exercise Capacity following Exercise Training

The mean values for the cardiopulmonary variables obtained during the SL-GXT are summarized in Table 4.11. The absolute mean VO_{2peak} observed prior to the 16 week period (PRE) was similar between groups (TR: 1176±370; NTR: 1195±403 $ml.min^{-1}$). The PRE mean VO_{2peak} per kilogram of body weight was also not statistically different between groups (TR: 12.15±3.48; NTR: 12.71±3.68 $ml.kg^{-1}.min^{-1}$). Following 16 weeks (POST) the mean absolute VO_{2peak} increased 24% in TR, with no change in NTR (TR: 1478±396; NTR: 1164±380 $ml.min^{-1}$) (see Figure 4.13). This increase was significantly different from NTR and PRE ($p \leq 0.05$). The average relative VO_{2peak} for TR increased 26%, from 12.15±3.48 $ml.kg^{-1}.min^{-1}$ to 16.05±4.23 $ml.kg^{-1}.min^{-1}$, and was also significantly different from PRE and NTR ($p \leq 0.05$).

The PRE values for VE_{peak} also were similar between groups (TR: 47.55±10.18; NTR: 47.93±11.01 $L.min^{-1}$). However, at POST the mean VE_{peak} was significantly higher for TR compared to NTR and PRE (TR: 61.25±10.38; NTR: 47.60±9.85 $L.min^{-1}$) ($p \leq 0.05$). The percent change in VE_{peak} was 27% and 25% compared to PRE and NTR, respectively. Yet, despite the increase in VO_{2peak} and VE_{peak} following the training period, the VE/VO_2 did not change (TR: 42.44±13.28; NTR: 40.89±11.85).

Exercise Tolerance and Time following Exercise Training

The RPE, clinical symptoms, and peak exercise time achieved during the SL-GXT, PRE and POST, are summarized in Table 4.12. The PRE mean values for perceived exertion, angina, and dyspnea at peak exercise were similar between groups. There was no change noted in the clinical symptoms during the SL-GXT after the 16 week period (TR: RPE=17±3, Angina=2.5±0.6, Shortness of Breath=2.5±0.7; NTR: RPE=16±3, ANG=2.3±0.8, DYSP=3.0.±0.2).

The PRE mean exercise time on the modified Naughton exercise protocol was also similar for both groups (TR: 12.34±3.47; NTR: 11.84±3.37 min). However, POST values for exercise time increased significantly (31%) in TR compared to PRE and NTR (TR: 16.22±4.62; NTR: 12.05±3.67 min) ($p \leq 0.05$) (see Figure 4.14).

Cardiac Function and Exercise Training

The PRE mean HR_{prex} was similar for both groups (TR: 72±16; NTR: 69±11 beats.min^{-1}). After 16 weeks the average HR_{prex} decreased slightly in TR, whereas there was no change in NTR (TR: 67±12; NTR: 69±10 beats.min^{-1}). However, the decrease did not reach statistical significance. The PRE mean HR_{peak} also was similar between groups (TR: 127±25; NTR: 125±17 beats.min^{-1}). Following 16 weeks there was a small rise in HR_{peak} in TR, with no change in NTR (TR: 133±26; NTR: 125±16 beats.min^{-1}). Again the, small change was not statistical significant. However, as a result of these small changes in HR_{prex} and HR_{peak}, the mean difference in chronotropic reserve was greater in TR compared to NTR (TR: 64 ± 9; NTR: 54 ± 9 beats.min^{-1}).

Peak exercise myocardial oxygen demand was similar for both groups at PRE (TR: 211±53; NTR: 205±41 [beats.min^{-1} * systolic blood pressure]/100). Exercise training resulted in an increase of 12% in peak exercise myocardial oxygen demand compared to PRE, with no changes noted in NTR (TR: 238±65; NTR: 211±70 [beats.min^{-1} * systolic blood pressure]/100). The PRE O_2pulse_{peak} was also similar for both groups (TR: 9.83±2.14; NTR: 9.57±1.94 ml.beat^{-1}). Yet, following exercise training there was a significant increase in O_2pulse_{peak} in TR (TR: 11.23±2.04; NTR: 9.47±1.94 ml.beat^{-1}) compared to PRE and NTR ($p \leq 0.05$).

Values for the cardiac responses obtained during the submaximal exercise test are summarized in Table 4.13. The pattern of the cardiac responses appear to be similar to those observed during the acute study. However, the evaluation of cardiac function following exercise training was significantly hindered by technical difficulties and the different number of patients in whom adequate cardiac images were obtained. Therefore, no statistical comparison of the cardiac responses following training was performed.

Circulatory Function and Exercise Training

The mean values for the circulatory responses to chronic exercise training are summarized in Table 4.11.

Resting and peak blood pressure responses following exercise training

The mean resting [(PRE: TR: 122±15 / 75±9 mmHg; NTR: 125±18 / 77±11 mmHg) (POST: TR: 119±19 / 74±9 mmHg; NTR: 129±18 / 79±10 mmHg)] and peak [(PRE: TR: 167±18 / 84±9 mmHg; NTR: 165±22 / 89±13 mmHg) (POST: TR: 178±20 /

86±9 mmHg; NTR: 168±25 / 91±16 mmHg)] systolic and diastolic blood pressure values were similar for both groups throughout the study. As a result the MAP at peak exercise, before and after the 16 weeks of intervention were also similar between groups (TR: 115±19; NTR: 117±22 mm Hg).

Relative changes in blood volume, cell volume, and plasma volume following exercise training

The relative changes in blood volume, cell volume, and plasma volume following exercise training were not altered with training. As described above, the SL-GXT was associated with a significant change in hemoconcentration. Hematocrit, Hb, and plasma protein increased with corresponding decreases in plasma volume and blood volume. The average pre (TR:39.57±0.87%; NTR:40.33±0.85%) and peak exercise (TR:41.40±0.87%; NTR:42.3±0.94%) hematocrit (corrected) and pre (TR:16.73±0.76; NTR:17.03±0.76 g/dl) and peak exercise (18.67±1.07 and 18.45±1.23 g/dl) Hb were similar between groups at PRE. Plasma protein concentration increased similarly for both groups from pre to peak exercise (TR:7.09±0.13 to 7.51±0.24; NTR:7.11±0.16 to 7.59±0.23 g/dl), indicating an approximate 7.5% increase ($p \leq 0.05$). Mean corpuscular hemoglobin concentration obtained by dividing Hb by hematocrit was 43.19±2.10 pre-exercise and 45.40±1.90 at peak exercise indicating a 4.9% increase ($p \leq 0.05$). The estimated blood volume (TR:8.1±1.01; NTR:8.3±1.11%) and plasma volume (TR:9.35±0.98; NTR:8.65±0.91) shift from pre-exercise to peak exercise were also similar for both groups. There was no difference in the pattern of these changes at POST, indicating a similar fluid efflux from the vascular compartment following exercise training.

Humoral responses following exercise training

Based on the relative changes in blood volume and plasma volume, the peak exercise neurohumoral concentrations were corrected for an 10.25% and 10.5% decrease in plasma volume at PRE and POST, respectively. Pre-exercise and peak exercise concentrations of the neuroendocrine hormones during the SL-GXT for TR and NTR are presented in Table 4.14 and Figure 4.15 to 4.18.

Angiotensin-aldosterone response to exercise training. The mean values for plasma angiotensin II_{prex} (TR: 5.6±1.3; NTR:4.8±1.2 pg•ml^{-1}) and $aldosterone_{prex}$ (TR: 158±38; NTR: 146±23 pg•ml^{-1}) were similar for both groups at PRE. The mean values for angiotensin II_{peak} (TR: 17.9±1.6; NTR: 16.37±2.2 pg•ml^{-1}) and $aldosterone_{peak}$ (TR: 202.4±51.6; NTR: 201.7±43.2 pg•ml^{-1}) were approximately 220% and 28% from the pre-exercise values, respectively, yet similar for both groups.

Following 16 weeks the mean angiotensin II_{peak} (TR: 20.5±1.6; NTR: 17.3±1.9 pg•ml^{-1}) and $aldosterone_{peak}$ (TR: 199.0±47.0; NTR: 209.0±39.0 pg•ml^{-1}) were similar to PRE values and between groups. However, mean values for plasma angiotensin II_{prex} (TR: 4.1±0.9 pg•ml^{-1}) and $aldosterone_{prex}$ (TR: 108±31 pg•ml^{-1}) were significantly reduced in TR compared to PRE values ($p \leq 0.05$), with no significant changes noted in angiotensin II_{prex} (NTR:5.0±1.2 pg.ml^{-1}) and $aldosterone_{prex}$ in NTR (NTR: 151±29 pg•ml^{-1}) (see Figure 4.15 and Figure 4.16). The percent decrease in POST angiotensin II_{prex} and $aldosterone_{prex}$ was 26% and 32% from the PRE values, respectively.

Arginine vasopressin response to exercise training. A similar finding was observed for arginine vasopressin. The PRE mean values for plasma arginine vasopressin$_{prex}$ were similar for both groups (TR: 6.1±1.7; NTR: 4.9±1.1 pg•ml^{-1}). With exercise AVP increased approximately 225% in both groups. The plasma arginine vasopressin$_{peak}$ was significantly different from plasma arginine vasopressin$_{prex}$ (TR: 17.9±4.5; NTR: 20.0±3.1 pg•ml^{-1}) ($p \leq 0.05$).

The POST mean values for plasma arginine vasopressin$_{prex}$ was significantly reduced in TR compared to PRE, whereas NTR remained unchanged (TR: 4.2±0.8 ;NTR: 5.1±1.3 pg•ml^{-1}). Yet, mean values for plasma arginine vasopressin$_{peak}$ remained similar to PRE in both groups (TR: 19.2±4.3; NTR: 21.4±2.8 pg•ml^{-1}) (see Figure 4.17). The percent decrease in POST arginine vasopressin$_{prex}$ compared to PRE values was 30%.

Atrial natriuretic peptide response to exercise training. The changes in neurohormones were also confirmed by evaluating the atrial natriuretic peptide response to exercise training. In fact, atrial natriuretic peptide responded similarly to the other hormones. The mean values for atrial natriuretic peptide$_{prex}$ were not statistically different between groups at PRE (TR: 37.2±8.0; NTR: 35.1±10.3 pg•ml^{-1}). Furthermore, atrial natriuretic peptide$_{peak}$ increased 95% (TR: 70.2±7.0; NTR: 68.3±12.5 pg•ml^{-1}) compared to pre-exercise values.

As observed for angiotensin II, aldosterone, and arginine vasopressin, a significant reduction in atrial natriuretic peptide$_{prex}$ was noted in TR compared to PRE, whereas the plasma atrial natriuretic peptide$_{prex}$ in NTR was unchanged (TR: 27.1±6.0; NTR:

36.5±11.2 pg•ml^{-1}). On the other hand, plasma atrial natriuretic peptide$_{peak}$ for TR and NTR increased similarly to PRE (TR: 66.8±7.4; NTR: 76.2±14.9 pg•ml^{-1}) (Figure 4.18). The percent decrease in plasma atrial natriuretic peptide$_{prex}$ was 27% compared to PRE values.

Skeletal Muscle Function and Exercise Training

Skeletal muscle strength, circumference and endurance

The mean values for calf muscle strength, circumference and endurance are presented in Table 4.15. The average calf muscle circumference for TR and NTR was not significantly different and remained unchanged throughout the experimental trial (TR: 35±7; NTR: 36±4 cm). Maximum voluntary contraction, as assessed by plantar flexion, was also similar for both groups (TR: 85±27; NTR: 86±30 psi). Exercise time was held constant (600 sec) for the low-intensity (25% MVC) experiment throughout the study. The mean exercise time for the high intensity workload was similar between groups at PRE (TR: 263±40; NTR: 267±43 sec). However, there was a significant increase in the mean exercise time for the high-intensity (85% MVC) workload in TR after training compared to PRE and NTR (TR: 362±45; NTR: 291±45 sec) ($p \leq 0.05$).

Skeletal muscle metabolic responses following exercise training

The mean values for the skeletal muscle metabolic responses (Pi, PCr, Pi/PCr, $H_2PO_4^-$, ATP/ADP*Pi, and ATP) at PRE and POST for TR and NTR are summarized in Table 4.16 and 4.17.

The effect of exercise training on the Pi / PCr ratio (low intensity). The Pi and PCr responses to low intensity exercise before and after the 16 week intervention are shown in Table 4.16. The PRE mean values for Pi/PCr_{prex} were similar for both groups (TR: 0.14±0.04; NTR: 0.12±0.04). With the onset of exercise the Pi/PCr ratio increased rapidly reaching a plateau after approximately 120 sec into the work bout, as previously noted. The average exercise Pi/PCr ratio (Pi/PCr_{ex}) was significantly different from Pi/PCr_{prex} ($p \leq 0.05$), yet similar between groups (TR: 0.66±0.09; NTR: 0.65±0.09). The average time at steady state was also similar for both groups (TR: 450±30; NTR: 435±40 sec) at PRE. In some patients the Pi/PCr ratio decreased slightly in the last minute of exercise. However, average Pi/PCr_{ee} remained significantly elevated above pre-exercise values (TR: 0.77±0.19; NTR: 0.72±0.12) ($p \leq 0.05$). The percent depletion in PCr (TR: 45.56±10.34; NTR: 41.07±14.54 %) and rise in Pi (TR: 153±28; NTR: 151±32 %), also were similar for both groups at PRE. The PCr_{res} (T1/2) are presented in Table 4.16. As previously shown the PCr_{res} was most rapid during the initial 60 to 120 sec. The PRE mean PCr_{res} (T1/2) (TR: 62±23; NTR: 61±27 sec) were similar between groups.

After the 16 week intervention the pattern of the Pi/PCr ratio was similar to PRE in both groups. The mean Pi/PCr_{prex} were not statistically different between groups (TR: 0.13±0.04; NTR: 0.14±0.02) and to PRE. The characteristic rapid rise in the Pi/PCr ratio with the onset of exercise and the average time at steady state were also similar for both groups (TR: 450±20; NTR: 430±40 sec) and not different from PRE. The average Pi/PCr_{ex} was significantly different from Pi/PCr_{prex} for both groups ($p \leq 0.05$). However,

whereas the average POST Pi/PCr_{ex} was similar to PRE values in NTR, the average POST Pi/PCr_{ex} was significantly lower for TR, compared to PRE, as depicted in Figure 4.19. Furthermore, as shown in Figure 4.20 the average Pi/PCr_{ex} was also significantly lower in TR compared to NTR (Tr: 0.52±0.08; NTr: 0.68±0.07) ($p \leq 0.05$). The change in the average Pi/PCr_{ex} in TR was the result of both a decrease in PCr depletion and rise in Pi for the same relative workload. The average Pi/PCr_{ee} was also significantly lower following training (TR: 0.53±0.10; NTR: 0.70±0.11) ($p \leq 0.05$). The percent difference between TR and NTR for the POST Pi/PCr_{ee} was 22±8 %. The mean PCr_{res} (T1/2) remained unchanged for NTR compared to PRE (NTR: 67±26 sec). In contrast, the mean PCr_{res} (T1/2) for TR decreased by 25%, compared to PRE (TR: 44±21 sec) ($p \leq 0.05$).

The effect of exercise training on intramuscular pH (low intensity). The PRE and POST mean values for muscle pH are presented in Table 4.16. The pH_{prex} were similar in both groups (TR:7.07±0.06; NTR: 7.10±0.05). The characteristic alkaline pattern was noted in both groups lasting approximately 90 sec followed by a gradual but steady decline in pH. The mean values for pH_{endex} (TR:6.99±0.10; NTR: 6.99±0.12) were similar between groups, yet significantly different from the pH values at 90 sec in the work bout ($p \leq 0.05$). Immediately following exercise a marked drop in muscle pH was observed in both groups. The average pH_{trough} following exercise occurred at approximately 120±35 sec in recovery (TR: 6.84±0.14; NTR: 6.89±0.16) and was significantly from pH_{prex} ($p \leq 0.05$). The pH_{trough} was followed by a gradual return to pre-exercise values during the remaining 12 to 13 min of recovery.

The mean POST pH_{prex} was similar for both groups (TR:7.12±0.06, and NTR 7.12±0.04). The brief period of alkalosis at the onset of exercise was statistically different from pH_{prex}. During exercise there was a non-significant trend toward a higher pH for TR (see Figure 4.21), whereas NTR showed a non significant trend toward a lower pH (Figure 4.21). However, pH_{endex} (TR: 7.04±0.24, and NTR 6.98±0.14) and pH_{endex} (TR: 7.00±0.24, and NTR 6.99±0.14) were not statistically different between groups.

The pH_{trough}, immediately following exercise was also similar between groups (TR: 6.89±0.11; NTR: 6.85±0.12). However, the pH_{trough} for TR occurred at 90 sec in recovery, whereas the pH_{trough} for NTR occurred at 150 sec in recovery. In addition, muscle pH recovery appeared to be faster in the trained group, yet was not significantly different from PRE.

The effect of exercise training on intramuscular $H_2PO_4^-$ (low intensity). The PRE and POST mean values for intramuscular $H_2PO_4^-$ are presented in Table 4.16. The pre-exercise mean values at PRE for $H_2PO_4^-$ during low intensity exercise, was similar between TR and NTR (TR: 1.54±0.19; NTR: 1.57±0.24). The percent increase in $H_2PO_4^-$ averaged over the entire work bout (TR: 190±42; NTR: 186±48%) and at end exercise (TR: 204±32; NTR: 202±22%) were also similar.

The POST pre-exercise mean values for $H_2PO_4^-$ during low intensity exercise were similar between TR and NTR (TR: 1.61±0.21; NTR: 1.52±0.21). The percent increase in $H_2PO_4^-$ was less pronounced in TR, when averaged over the entire workout (TR: 156±50; NTR: 188±53%), and at end exercise (TR: 187±28; NTR: 209±34%)

compared to NTR. Although the observed difference between TR and NTR were not statistically different between groups at POST, the mean difference for the average change during exercise was significant from PRE values in TR (see Figure 4.22).

The effect of exercise training on the phosporylation potential (ATP/ADP*Pi) (low intensity). The PRE and POST mean values for the phosphorylation potential are presented in Table 4.16. The mean pre-exercise values for ATP/ADP*Pi observed at PRE were similar for both groups prior to (TR:40.46±6.42; NTR: 43.37±5.63 mM^{-1}), and at end exercise (TR:8.24±1.51; NTR:10.60±1.93 mM^{-1}). The pattern of ATP/ADP*Pi was similar to what was previously described. With the onset of exercise the ATP/ADP*Pi ratio declined rapidly reaching steady state after approximately 120 sec. Mean ATP/ADP*Pi values at end-exercise were significantly different from pre-exercise values ($p \leq 0.05$) but similar between groups. The ATP/ADP*Pi (T1/2) were also similar between groups (TR: 66±21; NTR: 62±19 sec).

Following 16 weeks the mean values for ATP/ADP*Pi, prior to (TR:43.51±7.01; NTR: 40.46±6.22 mM^{-1}) and at the end of exercise (TR:12.97±1.74; NTR:9.58±1.61 mM^{-1}) were similar for both groups and to PRE values. However, whereas the ATP/ADP*Pi (T1/2) was not altered following 16 weeks in NTR, the mean recovery slopes were significantly faster for TR compared to NTR (TR: 29±13; NTR: 64±21 sec) ($p \leq 0.05$) (see Figure 4.23). In addition, the ATP/ADP*Pi (T1/2) in TR were approximately 48% faster compared to the rates observed at PRE.

The effect of exercise training on adenosine triphosphate (low intensity). Mean values at PRE for ATP prior to exercise were similar for both groups (TR:8.10±0.87; NTR:8.05±0.91mM). With exercise there was a slight decrease in mean ATP in both groups but this did not reach statistical significance (TR:7.59±1.45; NTR:7.51±1.26 mM). No significant changes in ATP were noted, prior to, during, and following the exercise bout for TR and NTR, following the 16 weeks.

Ratings of perceived exertion (low intensity). The mean end exercise RPE was similar between groups (TR: 15±2.5; NTR: 15±3.0). An average rating of 15 on the 15-grade scale indicates that the low intensity work load was perceived as *"Hard"*. Although, the end-exercise RPE was slightly lower in TR following training, no significant differences were noted at POST testing (TR: 13±4.0; NTR: 15±4.0).

The effect of exercise training on the Pi / PCr (high intensity). The effect of exercise training on the mean values for Pi/PCr before, during, and after exercise are presented in Table 4.17. The PRE Pi/PCr_{prex} was similar to low intensity and for both groups (TR: 0.13±0.04; NTR: 0.11±0.03). As depicted in Figure 4.24, the mean PRE Pi/PCr_{ee} was significantly elevated in both groups above pre-exercise values (TR: 1.92±0.48; NTR: 1.79±0.44) ($p \leq 0.05$) and the Pi/PCr_{ee} observed during low intensity. The percent decrease for PCr (TR: 65.64±13.24; NTR:65.25±14.30%) and increase for Pi (TR: 294±30; NTR: 280±39%) also were similar between groups. The mean PRE PCr_{res} (T1/2) (TR: 68.25±18.83; NTR: 66.57±28.74 sec) was not significantly different from the low intensity or between groups.

The mean POST Pi/PCr_{prex} was similar for both groups (TR: 0.14±0.04; NTR: 0.14±0.04) and to PRE values. The characteristic rapid rise in the Pi/PCr ratio with the onset of exercise was also similar for both groups. However, in contrast to the significant reduction noted in Pi/PCr_{ee} for TR during the low intensity exercise bout, no such difference was observed for the POST Pi/PCr_{ee} following the high intensity exercise bout (TR: 2.24±0.74; NTR: 1.85±0.61). Furthermore, the percent decrease for PCr (TR: 67.88±11.81; NTR:68.88±17.14%) and increase for Pi (TR: 302±28; NTR: 290±39%) also remained similar between groups. On the other hand, the mean PCr_{res} (T1/2) were significantly faster in TR following exercise training, compared to NTR (TR: 46.78±11.73; NTR: 71.42±20 sec). The percent improvement in PCr_{res} (T1/2) in TR was approximately 30% faster compared to PRE.

The effect of exercise training on intramuscular pH (high intensity). The effect of exercise training on the mean values for pH before, at peak, and after exercise are presented in Table 4.17 and Figure 4.25. The PRE mean values for pH_{prex} (TR:7.09±0.04; NTR: 7.08±0.04) and pH_{endex} (TR:6.82±0.09; NTR: 6.86±0.10) were similar for both groups. End exercise values for intramuscular pH were significantly different from pH_{prex} and pH_{endex} for low intensity ($p \leq 0.05$). The mean pH_{trough} occurred at approximately 110±30 sec in recovery (TR: 6.60±0.15; NTR: 6.59±0.14) and was significantly from the pH_{endex} ($p \leq 0.05$). The POST mean values for pH_{prex} (TR:7.07±0.04, and NTR 7.10±0.04), pH_{endex} (TR: 6.74±0.10, and NTR 6.80±0.12), and pH_{trough} (TR: 6.53±0.16; NTR: 6.61±0.15) were not statistically different between groups or from PRE.

The effect of exercise training on intramuscular $H_2PO_4^-$ (high intensity). The effect of exercise training on the mean values for $H_2PO_4^-$ before and at peak exercise are presented in Table 4.17 and Figure 4.26. The pre-exercise mean values at PRE for $H_2PO_4^-$ during high intensity exercise, were similar between TR and NTR (TR: 1.54±0.22; NTR: 1.81±0.34). The percent increase in $H_2PO_4^-$ at end exercise (TR: 584±132%; NTR: 532±121%) was also similar.

The POST pre-exercise mean values for $H_2PO_4^-$ during high intensity exercise was similar between TR and NTR (TR: 1.65±0.21; NTR: 1.62±0.21). However, at POST, the accumulation of $H_2PO_4^-$% decreased 30% in TR, with no significant change in NTR (TR:387±87; NTR:502±89%).

The effect of exercise training on the ATP/ADP*Pi (high intensity). The effect of exercise training on the mean values for the phosphorylation potential following exercise are presented in Table 4.17 and Figure 4.27. The PRE mean values for ATP/ADP*Pi prior to exercise (TR:39.71±5.98; NTR: 42.25±5.98 mM^{-1}) and at end exercise (TR:6.63±1.24; NTR:6.27±1.54 mM^{-1}) were similar for both groups. The ATP/ADP*Pi (T1/2) were also similar between groups (TR: 45.00±15.00; NTR: 48.00±19.00 sec) and to those observed for low intensity. The POST mean values, values for ATP/ADP*Pi, prior to exercise (TR:37.61±6.32; NTR: 38.27±5.74 mM^{-1}) and at end exercise (TR:6.27±1.54; NTR:5.80±1.10 mM^{-1}) also were similar for both groups and to PRE values. Yet, again, the ATP/ADP*Pi (T1/2) improved 38% in TR compared to NTR

(TR: 29±11; NTR: 51±21 sec) (Figure 4.27). In addition, the ATP/ADP*Pi (T1/2) was approximately 39% faster compared to the rates observed at PRE.

The effect of exercise training on adenosine triphosphate (high intensity). Mean values at PRE for ATP before- (TR:8.54±0.74; NTR:8.25±1.01 mM) and at end exercise were similar for both groups (TR:8.04±1.57; NTR:7.99±1.78 mM). No statistically significant changes in ATP were noted prior to and following the high intensity exercise bout for TR and NTR after the 16 week intervention.

Evaluation of Quality of Life

The Nottingham Health Profile scores before and after exercise training are presented in Table 4.18. The weighted scores for energy (TR:40.42±22.32; NTR:38.72±21.32), physical mobility (TR:22.62±12.32; NTR:23.84±13.39), and emotional reactions (TR:26.49±18.65; NTR:27.80±17.56) were similar for both groups at PRE. At T3 (POST), there was a consistent reduction in the weighted scores for energy (TR:10.66±11.02; NTR:39.77±20.32), physical mobility (TR:12.68±9.72; NTR:25.65±14.31), and emotional reactions (TR:11.91+17.65; NTR:29.41±18.23) in TR, with no change noted in NTR.

Table 4.1. Subject Characteristics		
Variables	Heart Failure (n=34)	Control (n=8)
Age (yrs)	61±6	63±6
Height (cm)	176±14	181±12
Weight (kg)	96±30	91±26
Fat%	27.35±7.40	25.12±5.62
Fat Weight (kg)	27.73±14.58	22.15±9.90
Duration of heart failure (yrs)	5±3	N/A
Etiology of heart failure	Ischemic Heart Disease	N/A
LVEF(%)	29.50±6.73	N/A
NYHA	2.45±0.49	N/A

Values are mean ± S.D.; LVEF=left ventricular ejection fraction; NYHA=New York Heart Association

Table 4.2. Cardiopulmonary Responses to Symptom-Limited Graded Exercise in Heart Failure Patients and Age-Matched Controls

Variables	Heart Failure (n=34)	Control (n=8)
VO_{2prex} ml.min^{-1}	299 ± 83	275 ± 56
VO_{2peak} ml.min^{-1}	1139 ± 123 *	2542 ± 156 *@
VO_{2prex} ml.kg^{-1}.min^{-1}	3.11 ± 0.78	2.91 ± 0.58
VO_{2peak} ml.kg^{-1}.min^{-1}	11.86 ± 3.52 *	30.57 ± 2.72 *@
VE_{prex} l.min^{-1}	13.09 ± 4.01	9.57 ± 2.27
VE_{peak} l.min^{-1}	45.41 ± 9.97	75.64 ± 15.28 *@
VE/VO_{2peak}	39.87 ± 8.23	29.76 ± 6.29 @
HR_{prex} beats.min^{-1}	73 ± 16	71 ± 10
HR_{peak} beats.min^{-1}	127 ± 25 *	155 ± 22 *@
$HR_{reserve}$ beats	54 ± 8	82 ± 11 @
SBP_{prex} mmHg	126 ± 17	120 ± 15
DBP_{prex} mmHg	76 ± 8	74 ± 9
SBP_{peak} mmHg	166 ± 15 *	191 ± 17 *@
DBP_{peak} mmHg	88 ± 9	82 ± 9
MAP_{prex} mmHg	93 ± 9	87 ± 8
MAP_{peak} mmHg	114 ± 10 *	104 ± 10 *
RPP_{peak}	207 ± 40	296 ± 35 *@
O_2 $Pulse_{peak}$ ml.beat^{-1}	4.37 ± 1.26	4.41 ± 1.02
O_2 $Pulse_{peak}$ ml.beat^{-1}	9.58 ± 2.14 *	16.41 ± 1.94 *@

Values are mean ± S.D.; VO_2=oxygen consumption per minute; VE=minute ventilation; HR=heart rate; SBP=systolic blood pressure; DBP=diastolic blood pressure; MAP=mean arterial pressure; RPP=rate pressure product; prex=pre-exercise

*$p \leq 0.05$ different from resting values,

@$p \leq 0.05$ different from HF values.

Table 4.3. Exercise Tolerance and Exercise Time during Symptom-Limited Graded Exercise in Heart Failure Patients	
Variables	Heart Failure
Rating of Perceived Exertion	16±3 (n=32)
Angina	2.5±1 (n=9)
Shortness of Breath	3.0±1 (n=28)
Exercise Time (min)	8.44±3.47(n=34)

Values are mean ± S.D.

Table 4.4. Cardiac Responses to Submaximal Exercise in Heart Failure Patients (n=34)

Variables	Supine	Standing	25% Heart Rate $_{peak}$	50% Heart Rate $_{peak}$	75% Heart Rate $_{peak}$
Heart Rate (Beats.min^{-1})	82 ± 9	88 ± 8	89 ± 11	108 ± 13*#	121 ± 16*#
Stroke Volume (ml)	79 ± 20	49 ± 22 *	72 ± 28 #	65 ± 27 #	62 ± 23
Cardiac Output (l.min^{-1})	6.54 ± 1.93	4.35 ± 1.67 *	6.41 ± 2.80 #	7.00 ± 2.72 #	7.52 ± 2.93 #

Values are mean ± S.D.;
*$p \leq 0.05$ vs. Supine;
#$p \leq 0.05$ vs. Standing

Table 4.5. Relative Changes in Blood Volume, Cell Volume, and Plasma Volume following Symptom-Limited Graded Exercise in Heart Failure Patients (n=19)

Variables	Pre-Exercise	Peak-Exercise	Percent Difference
Hematocrit (%)	43.30 ± 3.40	44.90 ± 3.42*	3.70
Hematocrit * 0.91 (%)	39.40 ± 3.92	40.9 ± 3.48*	3.80
Hemoglobin ($g.dl^{-1}$)	16.77 ± 3.47	18.48 ± 4.53*	8.90
Plasma Protein ($g.dl^{-1}$)	7.11 ± 1.26	7.61 ± 1.20*	7.03
Mean Corpuscular Hemoglobin	43.19 ± 2.10	45.40 ± 1.90*	4.90
Blood Volume (ml)	100.00	91.62 ± 1.20*	- 8.40
Cell Volume (ml)	39.42 ± 0.890	37.45 ± 0.80*	- 5.00
Plasma Volume (ml)	60.58 ± 0.90	54.19 ± 0.80*	- 10.55

Values are mean ± S.D.;
*$p \leq 0.05$ vs. Pre-Exercise

Table 4.6. Neurohumoral Responses to Symptom-Limited Graded Exercise in Heart Failure Patients (n=19)

Variables	Pre-Exercise	Peak-Exercise	% Increase from Pre-Exercise
Angiotensin II ($pg \cdot ml^{-1}$)	5.2±1.2	14.3±1.9*	175
Aldosterone ($pmol \cdot l^{-1}$)	152±31	169.1±52	11.25
Arginine Vasopressin ($pg \cdot ml^{-1}$)	6.0±1.6	15.8±3.7*	163
α-Atrial Natriuretic Peptide ($pg \cdot ml^{-1}$)	36.0±9.0	57.6±13.7*	60

Values are mean ± S.D.; *$p \leq 0.05$ vs. Pre-Exercise

Table 4.7. Maximal Voluntary Contraction, Calf Muscle Circumference, Exercise Time, and Ratings of Perceived Exertion in Heart Failure Patients and Age-Matched Controls

Variables	Heart Failure (n=34)	Control (n=8)
Maximal Voluntary Contraction (psi)	86 ± 21	93 ± 24
Calf Muscle Circumference (cm)	36 ± 5	35 ± 5
Exercise Time (sec) (Low Intensity)	600	600
Rating of Perceived Exertion (Low Intensity)	15 ± 2.5	11 ± 2.8 [@]
Exercise Time (sec) (High Intensity)	253 ± 20	405 ± 30 [@]
Rating of Perceived Exertion (High Intensity)	18 ± 2.5	18 ± 2.0

Values are mean ± S.D.
[@] $p \leq 0.05$ from heart failure.

Table 4.8. Skeletal Muscle Metabolic Responses to Low-Intensity (25%MVC) Work in Heart Failure Patients and Age-Matched Controls

Variables	Heart Failure (n=34)	Controls (n=8)
Pi mM		
Pre-Exercise	4.89 ± 1.22	4.58 ± 1.54
End-Exercise	12.98 ± 2.41 *	8.89 ± 1.95 *@
Pi (% Rise)	144.00 ± 9.00	95.00 ± 7.00 @
PCr mM		
Pre-Exercise	39.05 ± 3.82	38.71 ± 3.14
End-Exercise	19.15 ± 3.92 *	28.81 ± 2.99 *@
Recovery Rate (sec)	62.00 ± 27.00	26.50 ± 13.00
PCr (% Depletion)	43.40 ± 4.62	25.09 ± 3.80 @
Pi/PCr		
Pre-Exercise	0.13 ± 0.04	0.12 ± 0.03
End-Exercise	0.67 ± 0.10 *	0.31 ± 0.08 *@
pH		
Pre-Exercise	7.09±0.04	7.10±0.04
End-Exercise	6.99±0.10	7.10±0.07
Trough	6.89±0.10 *	7.01±0.08
$H_2PO_4^-$		
Pre-Exercise	1.54±0.19	1.53±0.23
End-Exercise	4.65±1.32 *	2.66±1.08 *@
$H_2PO_4^-$ (% Rise)	201±32	76±22 @
ATP (mM)		
Pre-Exercise	8.83±0.84	8.85±0.94
End-Exercise	8.45±0.75	8.83±0.61
ATP/ADP*Pi		
Pre-Exercise	40.46 ± 6.22	42.58 ± 5.54
End-Exercise	9.58 ± 1.61 *	13.32 ± 1.95 *
Recovery Rate (sec)	64.00 ± 21.00	31.50 ± 10.00 @

Values are mean ± S.D.; Pi=inorganic phosphate; PCr=phosphocreatine; $H_2PO_4^-$= diprotonated inorganic phosphate; ATP=adenosine triphosphate

*$p \leq 0.05$ from Pre-Exercise (prex);

@$p \leq 0.05$ from Heart Failure

Table 4.9. Skeletal Muscle Metabolic Responses to High-Intensity (85%MVC) Work in Heart Failure Patients and Age-Matched Controls

Variables	Heart Failure (n=34)	Controls (n=8)
Pi mM		
Pre-Exercise	4.59 ± 1.02	4.68 ± 1.76
End-Exercise	17.98 ± 3.31 *	13.86 ± 1.75 *@
Pi (% Rise)	292.00 ± 14.00	196.00 ± 12.00 @
[PCr] mM		
Pre-Exercise	38.55 ± 3.82	36.31 ± 4.02
End-Exercise	13.11 ± 4.00 *	13.81 ± 3.99 *
Recovery Rate (sec)	68.50 ± 24.00	29.50 ± 13.00 @
PCr (% Depletion)	64.00 ± 5.50	63.00 ± 4.80
Pi/PCr		
Pre-Exercise	0.11 ± 0.03	0.12 ± 0.03
End-Exercise	1.56 ± 0.36 *	1.00 ± 0.19 *@
pH		
Pre-Exercise	7.08±0.04	7.11±0.01
End-Exercise	6.85±0.09 *	6.89±0.06 *
Trough	6.59±0.13 *	6.62±0.09 *
$H_2PO_4^-$		
Pre-Exercise	1.43±0.25	1.63±0.21
End-Exercise	8.46±2.10 *	5.76±1.28 *@
$H_2PO_4^-$ (% Rise)	542±145	299±102 @
ATP (mM)		
Pre-Exercise	8.16±0.97	8.45±0.87
End-Exercise	8.65±0.76	8.73±0.69
ATP/ADP*Pi		
Pre-Exercise	40.63 ± 5.58	44.58 ± 5.54
End-Exercise	6.20 ± 2.09 *	7.18 ± 2.98 *
Recovery Rate (sec)	51 ± 19	21.00 ± 8.00@

Values are mean ± S.D.; Pi=inorganic phosphate; PCr=phosphocreatine; $H_2PO_4^-$ = diprotonated inorganic phosphate; ATP=adenosine triphosphate

*$p \leq 0.05$ from Pre-Exercise (prex);

@$p \leq 0.05$ from Heart Failure.

Table 4.10. Patient Characteristics for Exercise Training		
Variables	Training (n=14)	Non-Training (n=14)
Age (yrs)	61±7	62±8
Height (cm)	172±16	178±14
Weight (kg)	96±29	94±31
Fat%	28.00±6.00	27.00±7.00
Fat Weight (kg)	27.73±14.58	26.75±10.90
Duration of heart failure (yrs)	5±3	6±3
Etiology of heart failure	Ischemic Heart Disease	Ischemic Heart Disease
LVEF(%)	29.96±6.73	29.38±7.05
NYHA	2.38±0.49	2.50±0.50
Post Myocardial Infarction	n=13	n=12
Post Coronary Bypass	n=8	n=7
Hypertension	n=5	n=7
Diabetes Mellitus	n=3	n=4
Pharmaco-Therapy:		
Digitalis Glycosides	n=10	n=10
ACE-Inhibitors	n=9	n=8
Diuretics	n=10	n=11
Anticoagulants	n=6	n=4
Antihyperlipidemics	n=3	n=4
Beta-Blockers	n=3	n=2

Values are mean ± S.D.; LVEF=left ventricular ejection fraction; NYHA=New York Heart Association

Table 4.11. Cardiopulmonary Responses before and after Exercise Training in Heart Failure Patients

	Training (n=14)		Non-Training (n=14)	
Variables	PRE	POST	PRE	POST
VO_{2peak} ml.min^{-1}	1176 ± 370	1478 ± 396 #@	1195 ± 403	1164 ± 380
VO_{2peak} ml.kg^{-1}.min^{-1}	12.15 ± 3.48	16.05 ± 4.23#@	12.71 ± 3.68	12.03 ± 4.50
VE_{peak} l .min^{-1}	47.55 ± 10.18	61.25 ± 0.38#@	47.93 ± 11.01	47.60 ± 9.85
VE / VO_{2peak}	41.43 ± 11.18	42.44 ± 13.28	40.10 ± 9.01	40.89 ± 11.85
HR_{prex} beats.min^{-1}	72 ± 16	69 ± 11	67 ± 12	69 ± 10
HR_{peak} beats.min^{-1}	127 ± 25	133 ± 26 *	125 ± 17 *	126 ± 16 *
$HR_{reserve}$ beats	55 ± 10	64 ± 9	56 ± 9	54 ± 9
SBP_{prex} mm Hg	122 ± 15	119 ± 19	125 ± 18	129 ± 18
DBP_{prex} mm Hg	75 ± 9	74 ± 9	77 ± 11	79 ± 10
SBP_{peak} mm Hg	167 ± 18 *	178 ± 20 *	165 ± 22 *	168 ± 25 *
DBP_{peak} mm Hg	84 ± 9	86 ± 9	89 ± 13	91 ± 16
MAP_{prex} mm Hg	95 ± 11	91 ± 13	92 ± 18	96 ± 17
MAP_{prex} mm Hg	111 ± 15 *	115 ± 19 *	113 ± 19 *	117 ± 22 *
RPP_{peak}	211 ± 53	238 ± 65	205 ± 41	211 ± 70
O_2 $Pulse_{peak}$ ml.beat^{-1}	9.38 ± 2.14	11.23 ± 2.04#@	9.57 ± 1.94	9.47 ± 1.94

Values are mean ± S.D.; VO_2=oxygen consumption per minute; VE=minute ventilation; HR=heart rate; SBP=systolic blood pressure; DBP=diastolic blood pressure; MAP=mean arterial pressure; RPP=rate pressure product; prex=pre-exercise

*$p \leq 0.05$ from pre-exercise (prex);

#$p \leq 0.05$ different from PRE;

@$p \leq 0.05$ different from NTR.

Table 4.12. Exercise Tolerance and Exercise Time before and after Exercise Training in Heart Failure Patients

	Training (n=14)		Non-Training (n=14)	
Variables	PRE	POST	PRE	POST
Rating of perceived exertion	16±3	17±5	17±4	16±3
Angina	2.4±0.9	2.5±0.6	2.5±0.8	2.3 ±0.8
Shortness of Breath	3.0±0.3	2.5±0.7	2.7±0.6	3.0±0.2
Exercise Time (min)	12.34±3.47	16.22±4.62 # @	11.84±3.37	12.05±3.67

Values are mean ± S.D.;
$p \leq 0.05$ different from PRE;
@ $p \leq 0.05$ different from NTR.

Table 4.13. Cardiac Responses to Submaximal Exercise Following Exercise Training in Heart Failure Patients

Variables	Supine		Standing		25% Heart Rate $_{peak}$		50% Heart Rate $_{peak}$		75% Heart Rate $_{peak}$	
	PRE (n=10)	POST (n=8)	PRE (n=9)	POST (n=6)	PRE (n=7)	POST (n=4)	PRE (n=6)	POST (n=4)	PRE (n=5)	POST (n=3)
Heart Rate (Beats.min^{-1})	85 ±10	82 ±13	89 ±11	86 ±12	90 ±10	89 ±12	104 ±15	107 ±18	119 ±16	117 ±18
Stroke Volume (ml)	76 ±20	73 ±24	42 ± 19	45 ±22	69 ± 30	68 ± 26	68 ± 29	66 ± 24	66 ± 18	64 ± 20
Cardiac Output (L.min^{-1})	6.3 ±1.7	6.5 ±2.0	3.9 ±1.8	4.0 ±1.8	6.3 ±2.1	6.5 ±2.2	7.1 ±2.4	7.1 ±2.6	7.9 ±2.7	7.8 ±2.5

Values are mean ± S.D.

Table 4.14. Neurohumoral Response before and after Exercise Training in Heart Failure Patients

	Training (n=11)		Non-Training (n=10)	
Variables	PRE	POST	PRE	POST
Angiotensin II_{prex} (pg . ml^{-1})	5.6±1.3	4.1±0.9#	4.8±1.2	5.0±1.2
Angiotensin II_{peak} (pg . ml^{-1})	17.9±1.6 *	20.5±1.6 *	16.4±2.2 *	17.3±1.9 *
$Aldosterone_{prex}$ ($pmol.l^{-1}$)	158±38	108±31#	146±23	151±29
$Aldosterone_{peak}$ ($pmol.l^{-1}$)	203±51	199±47 *	202±43	209±39
$Arginine\ Vasopressin_{prex}$ (pg . ml^{-1})	6.1±1.7	4.2±0.8 #	4.9±1.1	5.1±1.3
$Arginine\ Vasopressin_{peak}$ (pg . ml^{-1})	17.9±4.5 *	19.2±4.3 *	20.0±3.1 *	21.4±2.8 *
α-Atrial Natriuretic $Peptide_{prex}$ (pg . ml^{-1})	37.2±8.0	27.1±6.0 #	35.1±10.3	36.5±11.2
α-Atrial Natriuretic $Peptide_{peak}$ (pg . ml^{-1})	70.2±7.0 *	66.8±7.4 *	68.3±12.5 *	76.2±14.9 *

Values are mean ± S.D.;
*$p \leq 0.05$ from pre-exercise (prex);
#$p \leq 0.05$ from PRE.

Table 4.15. Maximal Voluntary Contraction, Calf Muscle Circumference, Exercise Time, and Perceived Exertion before and after Exercise Training in Heart Failure Patients

	Training (n=14)		Non-Training (n=14)	
Variables	PRE	POST	PRE	POST
Maximal Voluntary Contraction (psi)	85 ± 27	88 ± 34	86 ± 30	84 ± 32
Calf Muscle Circumference (cm)	35 ± 7	36 ± 8	36 ± 4	36 ± 7
Exercise Time (sec) (Low Intensity)	600	600	600	600
Rating of Perceived Exertion (Low Intensity)	15 ± 2.5	13 ± 4	15 ± 3	15 ± 4
Exercise Time (sec) (High Intensity)	263 ± 40	362 ± 45 #	267 ± 43	291 ± 45
Rating of Perceived Exertion (High Intensity)	18 ± 2.5	18± 2	17 ± 3	17 ± 2

Values are mean ± S.D.;
$p \leq 0.05$ from PRE.

Table 4.16. Skeletal Muscle Metabolic Responses to Low-Intensity (25%MVC) Work before and after Exercise Training in Heart Failure Patients

	Training (n=14)		Non-Training (n=14)	
Variables	PRE	POST	PRE	POST
Pi/PCr				
Pre-Exercise	0.14 ± 0.04	0.13 ± 0.04	0.12 ± 0.04	0.14 ± 0.02
Average-Exercise	0.66 ± 0.09*	0.53 ± 0.08*#@	0.65 ± 0.13*	0.68 ± 0.11*
End-Exercise	0.77 ± 0.19*	0.53 ± 0.10*#@	0.72 ± 0.12	0.70 ± 0.11
Pi				
% Rise	153.00 ± 28.00	115.00± 25.00	151.00 ± 32.00	142.00 ± 26.00
PCr				
%Depletion	45.56 ± 10.34	37.17 ± 9.85	41.07 ± 14.54	42.68 ± 15.67
Resynthesis Rate (sec)	63.25 ± 19.34	46.87±14.34#@	61.59 ± 20.74	66.65 ± 20.98
pH				
Pre-Exercise	7.07±0.06	7.11±0.06	7.10±0.05	7.10±0.05
End-Exercise	6.99±0.10*	7.04±0.14*	6.99±0.12*	6.98±0.14*
Trough	6.84±0.11*	6.89±0.11*	6.89±0.13*	6.85±0.13*
$H_2PO_4^-$				
Pre-Exercise	1.54±0.19	1.61±0.21	1.57±0.24	1.52±0.21
End-Exercise	4.91±1.32*	4.60±1.09*	4.34±1.42*	4.55±1.27*
$H_2PO_4^-$ (%)				
Pre-Exercise	1	1	1	1
Average-Exercise	190 ± 42*	156 ± 50*	186 ± 48*	188 ± 53*
End-Exercise	204 ± 32*	187 ± 28*	202 ± 22*	209 ± 34*
ATP (mM)				
Pre-Exercise	8.10 ± 0.87	8.54 ± 0.80	8.05 ± 0.91	8.27 ± 0.84
End-Exercise	7.79 ± 1.45	8.25 ± 1.63	7.83 ± 1.57	7.99 ± 1.75
ATP/ADP*Pi				
Pre-Exercise	40.46 ± 6.42	43.51 ± 7.01	43.37 ± 5.63	40.46 ± 6.22
End-Exercise	8.24 ± 1.51*	12.97 ± 1.74*	10.60 ± 1.93*	9.58 ± 1.61*
Recovery Rate (sec)	66.00 ± 21.00	29.00±13.00#@	62.00 ± 19.00	64.00 ± 21.00

Values are mean ± S.D.; Pi=inorganic phosphate; PCr=phosphocreatine; $H_2PO_4^-$ = diprotonated inorganic phosphate; ATP=adenosine triphosphate

*$p \leq 0.05$ from pre-exercise (prex);

#$p \leq 0.05$ from PRE;

@$p \leq 0.05$ from NTR.

Table 4.17. Skeletal Muscle Metabolic Responses to High-Intensity (85%MVC) Work before and after Exercise Training in Heart Failure Patients

	Training (n=14)		Non-Training (n=14)	
Variables	PRE	POST	PRE	POST
Pi/PCr				
Pre-Exercise	0.13 ± 0.04	0.14 ± 0.04	0.11 ± 0.03	0.14 ± 0.04
End-Exercise	1.92 ± 0.48*	2.24 ± 0.74*	1.79 ± 0.44*	1.85 ± 0.61*
Pi				
% Rise	294.00 ± 30.00	302.00± 28.00	280.00 ± 39.00	290.00 ± 32.00
PCr				
%Depletion	65.64 ± 13.24	67.88 ± 11.81	65.25 ± 14.30	68.88 ± 17.14
Resynthesis Rate (sec)	68.25 ± 18.83	46.78 ± 11.73#	66.57 ± 28.74	71.42 ± 19.20
pH				
Pre-Exercise	7.09±0.04	7.07±0.05	7.08±0.05	7.10±0.04
End-Exercise	6.83±0.12*	6.74±0.10*	6.86±0.11*	6.83±0.13*
Trough	6.60±0.14*	6.53±0.15*	6.58±0.14*	6.61±0.15*
$H_2PO_4^-$				
Pre-Exercise	1.54±0.22	1.65±0.21	1.81±0.34	1.62±0.21
End-Exercise	10.14±2.65*	8.07±2.09*	9.49±2.98*	10.95±2.99*
$H_2PO_4^-$ (%)				
Pre-Exercise	1	1	1	1
End-Exercise	584 ± 132*	382 ± 88*#	532 ± 121*	521 ± 130*
ATP (mM)				
Pre-Exercise	8.54 ± 0.74	8.80 ± 1.20	8.25 ± 1.01	8.60 ± 1.32
End-Exercise	8.04 ± 1.57	8.35 ± 2.01	7.99 ± 1.78	8.32 ± 2.04
ATP/ADP*Pi				
Pre-Exercise	39.71 ± 5.98	37.61 ± 6.32	42.25 ± 5.98	38.27 ± 5.74
End-Exercise	6.63 ± 1.24*	6.59 ± 1.27*	6.27 ± 1.54*	5.80 ± 1.10*
Recovery Rate (sec)	45.00 ± 15.00	29.00 ± 11.00#	48.00 ± 19.00	51.00 ± 21.00

Values are mean ± S.D.; Pi=inorganic phosphate; PCr=phosphocreatine; $H_2PO_4^-$ = diprotonated inorganic phosphate; ATP=adenosine triphosphate

*$p \leq 0.05$ from pre-exercise (prex);

#$p \leq 0.05$ from PRE.

Table 4.18. Nottingham Health Profile Responses before and after Exercise Training in Heart Failure Patients

	Training (n=9)		Non-Training (n=12)	
Variables	PRE	POST	PRE	POST
Energy	40.42 ± 22.32	10.66 ± 9.02	38.72 ± 21.32	39.77 ± 20.32
Physical Mobility	22.62 ± 12.32	12.68 ± 9.72	23.84 ± 13.39	25.65 ± 14.31
Emotional Reaction	26.49 ± 18.65	11.91 ± 7.65	27.80 ± 17.56	29.41 ± 18.23

Values are mean ± S.D.

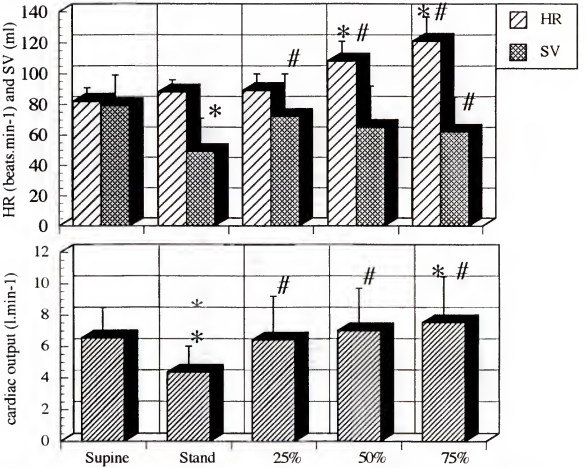

Figure 4.1. Mean±SD of the cardiac responses (HR=heart rate, SV=stroke volume and cardiac output) to a supine and standing (stand) position and three submaximal exercise intensities (25%, 50% and 75%) of HRpeak achieved on the SL-GXT in heart failure (n=34). *$p \leq 0.05$ from supine, #$p \leq 0.05$ from standing

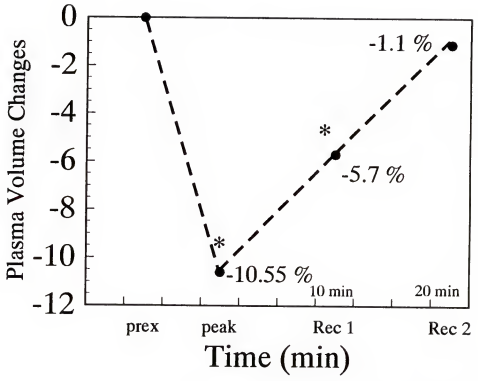

Figure 4.2. Magnitude and time course of fluid shift immediately following symptom-limited graded exercise and during recovery (Rec 1 and Rec 2) in heart failure (n=19). *p≤0.05 from prex.

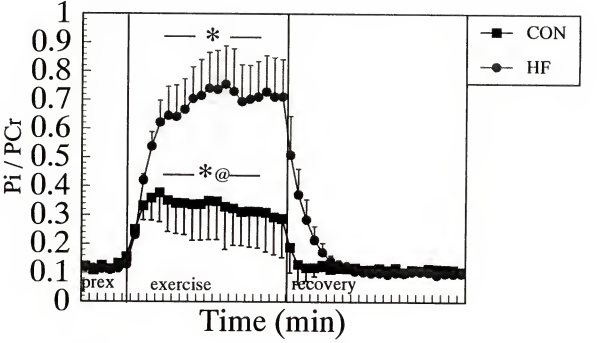

Figure 4.3. The mean±SE of the oxidative index (Pi/PCr) prior to exercise (prex), during, and immediately following low-intensity (25% MVC) plantar flexion in age-matched controls (CON; n=8) and heart failure (HF; n=34).
*p≤0.05 from prex; @p≤0.05 from HF.

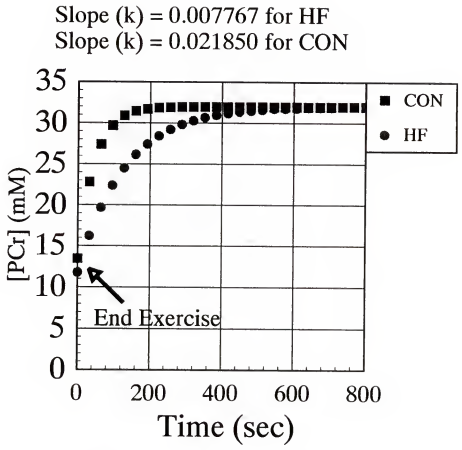

Figure 4.4. Example of the PCr recovery curves using a monoexponential curve fit (slope (k)), in a heart failure (HF) patient and age-matched control (CON), following high - intensity (85% MVC) plantar flexion.

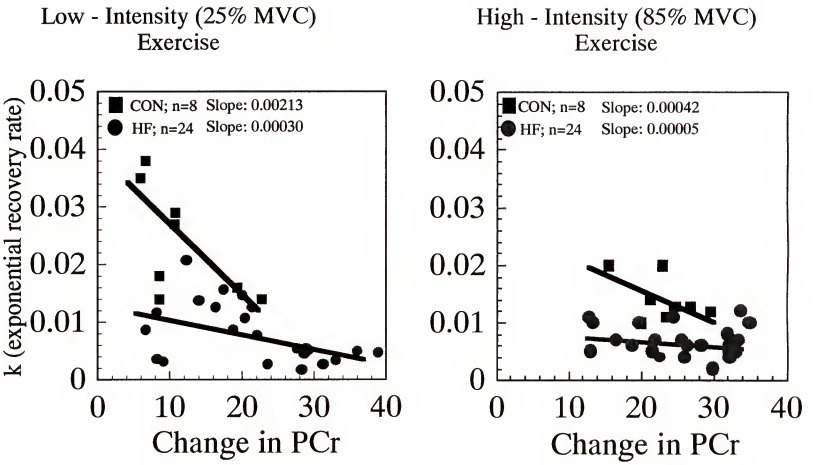

Figure 4.5. The relationship between the maximal level of PCr depletion at peak exercise and the exponential recovery rate following low - and high - intensity plantar flexion in age-matched controls (CON; n=8) and heart failure (HF; n=24).

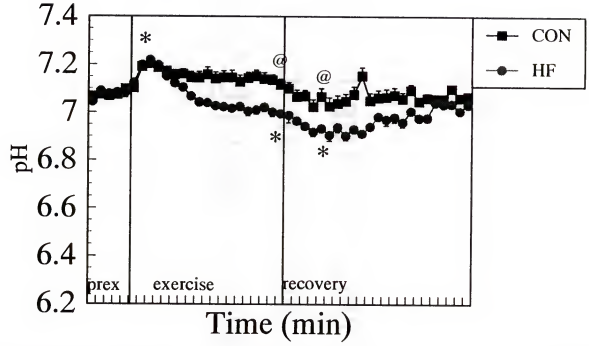

Figure 4.6. The mean±SE intramuscular pH prior to exercise (prex), during, and immediately following low-intensity (25% MVC) plantar flexion in age-matched controls (CON; n=8) and heart failure (HF; n=34).
*p≤0.05 from prex; @p≤0.05 from heart failure.

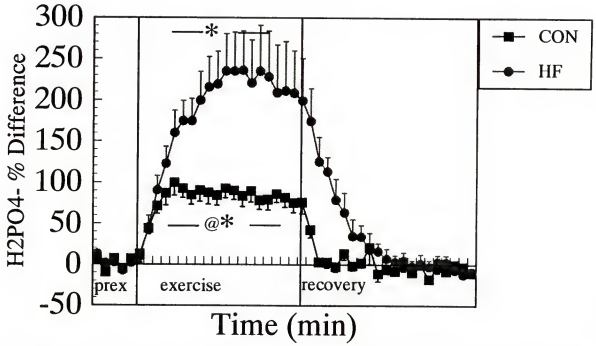

Figure 4.7. The mean±SE diprotonated form of Pi (H2PO4-) prior to exercise (prex), during, and immediately following low-intensity (25% MVC) plantar flexion in age-matched controls (CON; n=8) and heart failure (HF; n=34).
*p≤0.05 from prex; @p≤0.05 from heart failure.

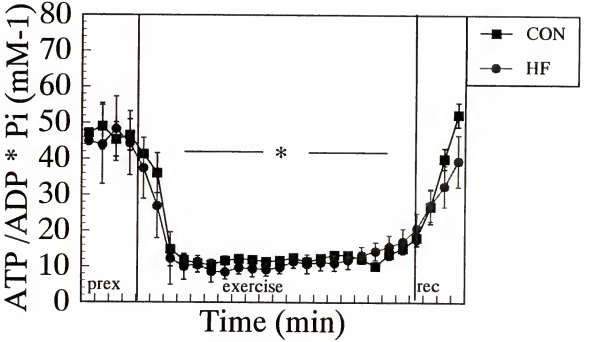

Figure 4.8. Mean±SE of the phosphorylation potential (ATP/ADP*Pi) prior to (prex), during low-intensity (25% MVC), and immediately following (rec) plantar flexion in age-matched controls (CON; n=8) and heart failure (HF; n=34).
*p≤0.05 from prex.

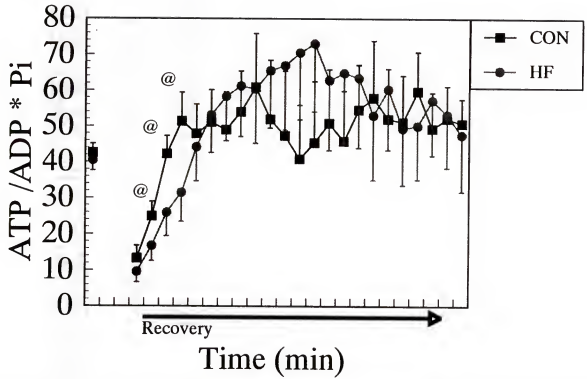

Figure 4.9. Mean±SE of the recovery slope of the phosphorylation potential (ATP/ADP*Pi) immediately following low-intensity (25% MVC) plantar flexion in age-matched controls (CON; n=8) and heart failure (HF; n=34).
@p≤0.05 from heart failure.

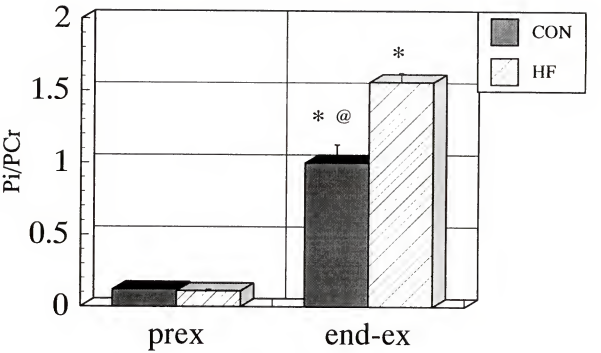

Figure 4.10. The mean±SE of the oxidative index (Pi/PCr) prior to (prex) and at the end of a fatiguing bout of high-intensity (85% MVC) plantar flexion (end-ex) in age-matched controls (CON; n=8) and heart failure (HF; n=34).
*p≤0.05 from prex; @p≤0.05 from heart failure.

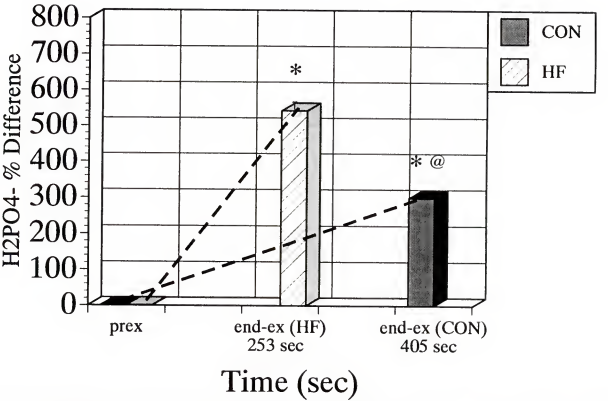

Figure 4.11. The mean±SE diprotonated form of Pi (H2PO4-), presented as a percent from prex, at the end of a fatiguing bout of high-intensity (85% MVC) plantar flexion in age-matched controls (CON; n=8) and heart failure (HF; n=34).
*p≤0.05 from prex; @p≤0.05 from heart failure.

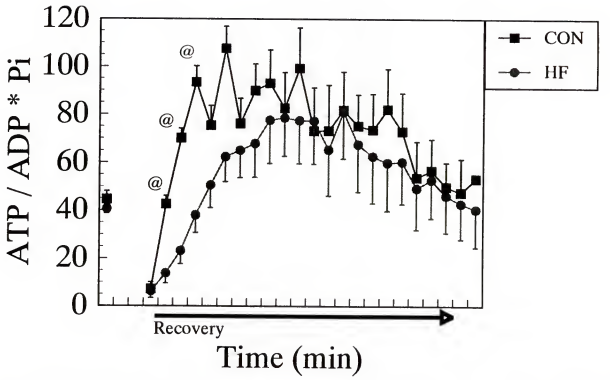

Figure 4.12. Mean±SE of the recovery slope of the phosphorylation potential (ATP/ADP*Pi) immediately following high-intensity (85% MVC) plantar flexion in age-matched controls (CON; n=8) and heart failure (HF; n=34).
@p≤0.05 from heart failure.

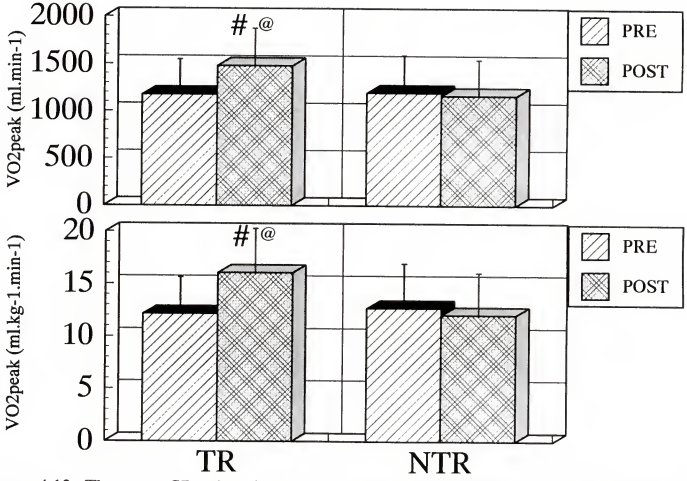

Figure 4.13. The mean±SD values for exercise capacity (VO2peak) before (PRE) and after 16 weeks (POST) of exercise training (TR; n=14) or usual care (NTR; n=14) in heart failure. #p≤0.05 from PRE; @p≤0.05 from NTR.

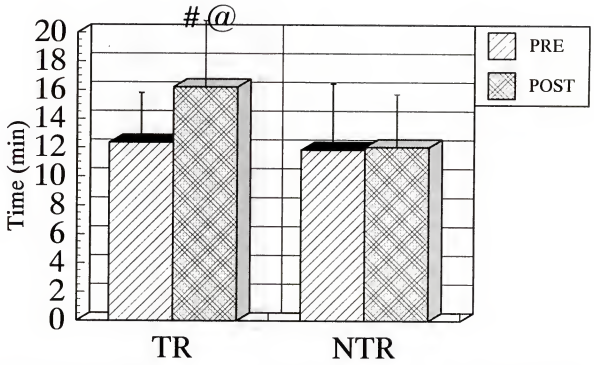

Figure 4.14. The mean±SD values for exercise time before (PRE) and after 16 weeks (POST) of exercise training (TR; n=14) or usual care (NTR; n=14) in heart failure. #p≤0.05 from PRE; @p≤0.05 from NTR.

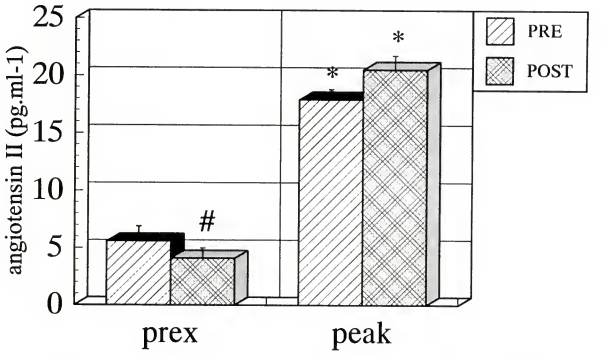

Figure 4.15. The mean±SD values for plasma angiotensin II before (PRE) and after 16 weeks (POST) of exercise training (TR; n=14) prior to (prex) and immediately (peak) following submaximal graded exercise in heart failure.
#p≤0.05 from PRE; *p≤0.05 from prex.

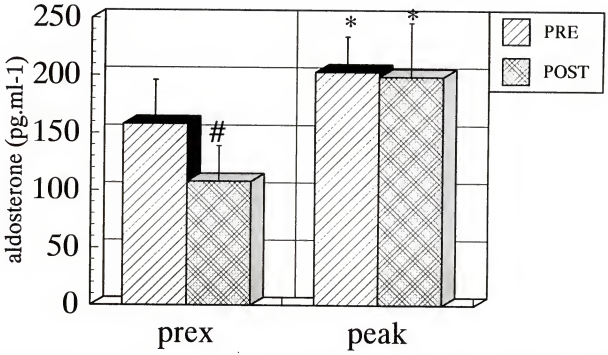

Figure 4.16. The mean±SD values for plasma aldosterone before (PRE) and after 16 weeks (POST)of exercise training (TR; n=14) prior to (prex) and immediately (peak) following submaximal graded exercise in heart failure.
#p≤0.05 from PRE; *p≤0.05 from prex.

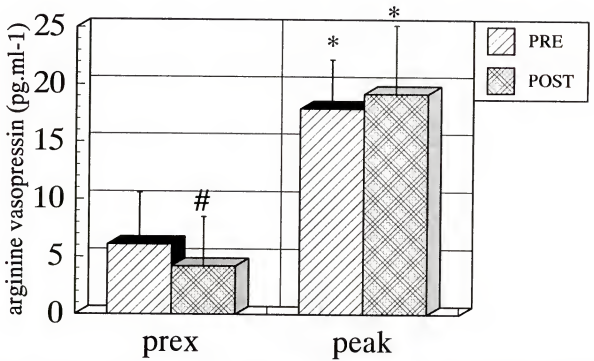

Figure 4.17. The mean±SD values for plasma arginine vasopressin before (PRE) and after 16 weeks (POST) of exercise training (TR; n=14) prior to (prex) and immediately (peak) following submaximal graded exercise in heart failure.
#p≤0.05 from PRE; *p≤0.05 from prex.

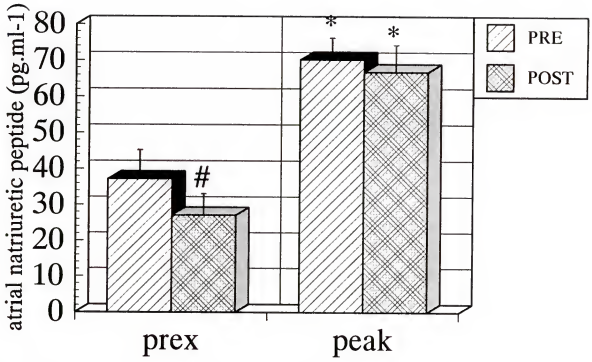

Figure 4.18. The mean±SD values for plasma atrial natriuretic peptide before (PRE) and after 16 weeks (POST) of exercise training (TR; n=14) prior to (prex) and immediately (peak) following submaximal graded exercise in heart failure.
#p≤0.05 from PRE; *p≤0.05 from prex.

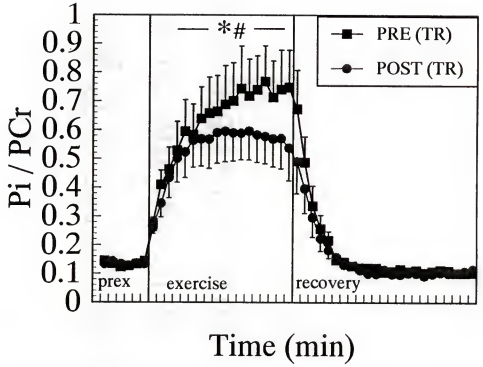

Figure 4.19. The effect of exercise training on the mean±SE of the oxidative index (Pi/PCr) prior to exercise (prex), during, and immediately following low-intensity (25% MVC) plantar flexion in heart failure.
*p≤0.05 from PRE (TR); #p≤0.05 from PRE; TR=Training (n=14).

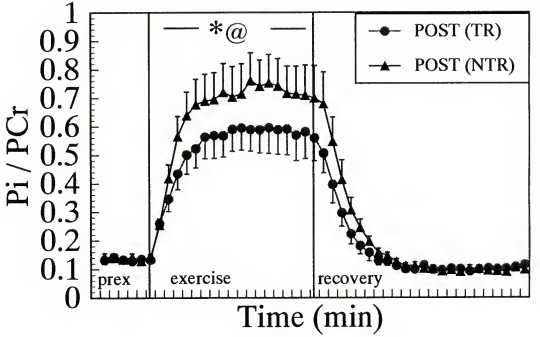

Figure 4.20. Mean±SE of the oxidative index (Pi/PCr) prior to exercise (prex), during, and immediately following low-intensity (25% MVC) plantar flexion in heart failure. *p≤0.05 from prex; @p≤0.05 from POST (NTR); NTR=non-training (n=14) and TR=Training (n=14).

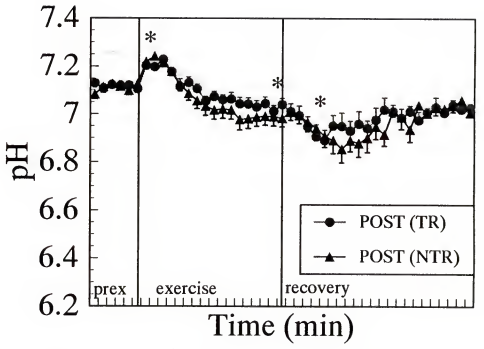

Figure 4.21. Mean±SE intramuscular pH prior to exercise (prex), during, and immediately following low-intensity (25% MVC) plantar flexion in heart failure.
*p≤0.05 from prex; NTR=non-training (n=14) and TR=Training (n=14).

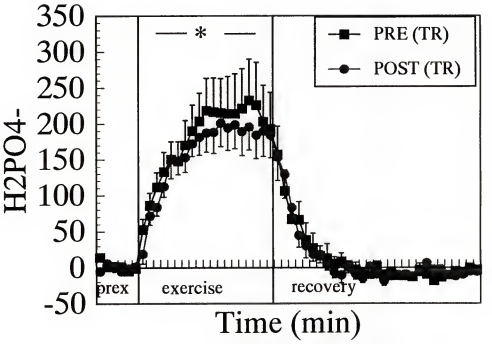

Figure 4.22. The effect of exercise training on the mean±SE diprotonated form of Pi (H2PO4-) prior to exercise (prex), during, and immediately following low-intensity (25% MVC) plantar flexion in heart failure.
*p≤0.05 from prex (TR); TR=Training (n=14).

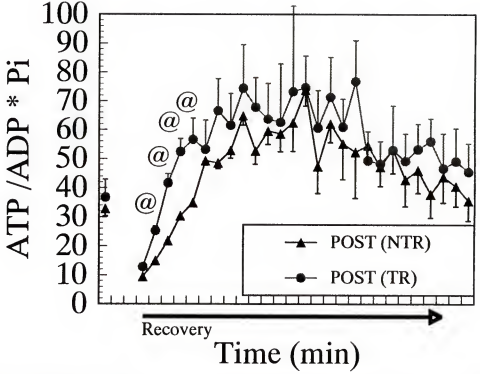

Figure 4.23. Mean±SE of the recovery slope of the phosphorylation potential (ATP/ADP*Pi) immediately following low-intensity (25% MVC) plantar flexion in heart failure. @p≤0.05 from POST (NTR); NTR=non-training (n=14) and TR=Training (n=14).

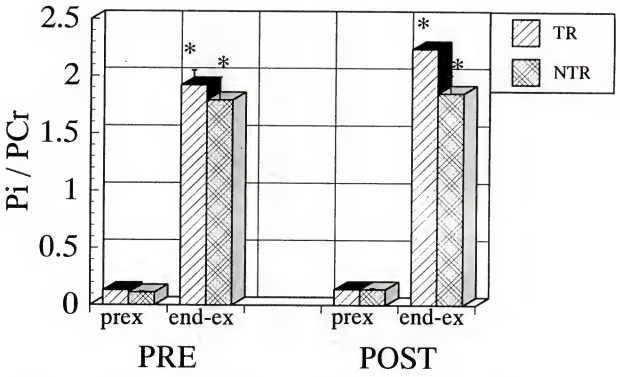

Figure 4.24. The mean±SE of the oxidative index (Pi/PCr) prior to exercise (prex), and at the end of a fatiguing bout of high-intensity (85% MVC) plantar flexion in heart failure. *p≤0.05 from PRE (TR); TR=Training (n=14); NTR=Non-training (n=14).

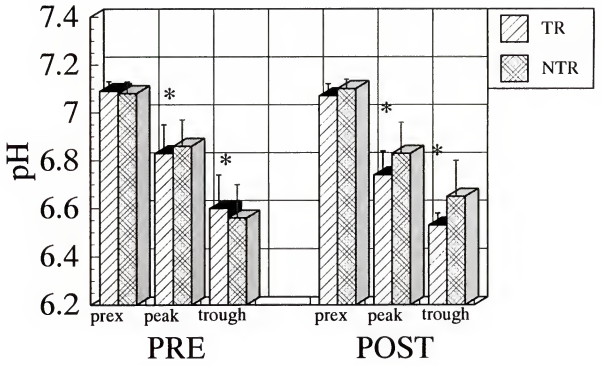

Figure 4.25. The mean±SE intramuscular pH prior to exercise (prex), at the end of exercise (peak), and at the post-exercise low (trough) following high-intensity (85% MVC) plantar flexion in heart failure.
*p≤0.05 from PRE (TR); TR=Training (n=14).

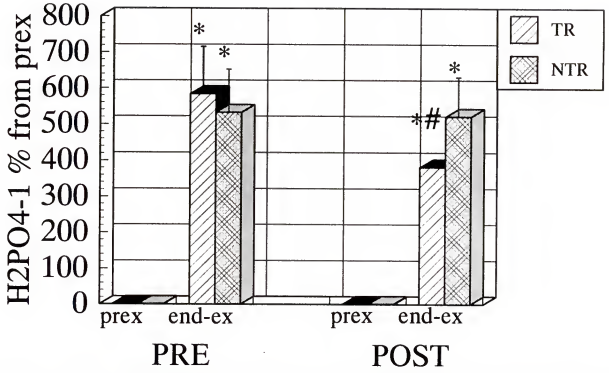

Figure 4.26. The mean±SE diprotonated form of Pi (H2PO4-), presented as a percent from prex, at the end of a fatiguing bout of high-intensity (85% MVC) plantar flexion in heart failure.

*p≤0.05 from prex (TR); #p≤0.05 from PRE; TR=Training (n=14).

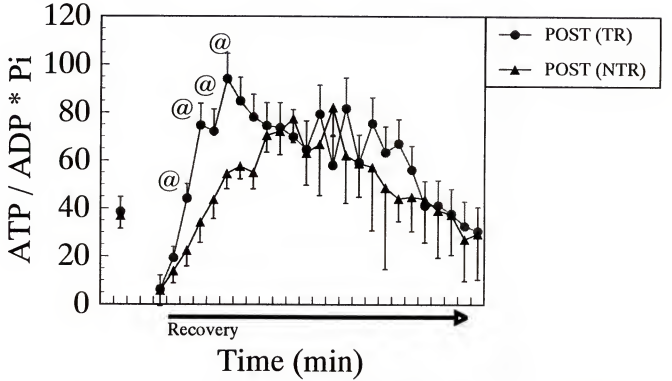

Figure 4.27. Mean±SE of the recovery slope of the phosphorylation potential (ATP/ADP*Pi) immediately following high-intensity (85% MVC) plantar flexion in heart failure. @p≤0.05 from POST (NTR); NTR=non-training (n=14) and TR=Training (n=14).

CHAPTER 5
DISCUSSION AND CONCLUSION

Introduction

The present study was designed to evaluate the cardiac, hemodynamic, neurohumoral, and skeletal muscle metabolic responses to exercise in patients with heart failure. The first part of the study specifically aimed to further determine the manner in which the characteristic time-dependent compensatory adaptations in heart failure respond to an acute bout of exercise. The specific objective of this part of the study was to determine the contribution of these compensatory adaptations to the clinical severity and exercise intolerance evident in the majority of patients with heart failure.

The second part of the study was designed to determine whether 16 weeks of exercise training could be an adequate stimulus to reverse some or all of the compensatory adaptations that contribute to the exercise intolerance in patients with heart failure. Specifically, the study was designed to determine if exercise training could result in (1) an increase in exercise tolerance and capacity, (2) an improvement in cardiac function, (3) a reversal of neurohumoral abnormalities, (4) a reversal of skeletal muscle abnormalities, and (5) improved quality of life.

The results of this study indicated a marked impaired exercise tolerance and capacity in patients with heart failure compared to a group of age-matched healthy

controls. Although there are several factors which could have contributed to the marked exercise intolerance, evidence from the present study identifies two important factors: (1) a reduction in cardiac, hemodynamic, and neurohumoral reserve capacity, and (2) abnormalities in skeletal muscle energetics. Furthermore, the results of this study demonstrated that patients with heart failure may benefit from a 16 week exercise program as evidenced by improved exercise performance, secondary to improved skeletal muscle energetics, a greater reserve capacity in hemodynamic and neurohumoral function, and quality of life.

In an attempt to provide an explanation of the findings of this study, the remainder of this discussion will focus on six specific areas including (1) comparing the results to the existing literature, (2) identifying the unique findings of this study, (3) the potential mechanism which could explain the findings, (4) the limitations of the study, (5) the clinical implications of this data, and (6) the future considerations and directions.

Exercise Capacity and Tolerance

Exercise capacity, as previously mentioned, has considerable prognostic value in patients with heart failure (Bittner et al., 1993; Cleland et al., 1987; Cohn & Rector, 1988; Likoff et al., 1987; Mancini et al., 1991; Parameshwar et al., 1992; Roul et al., 1994; Szlachcic et al., 1985). In the study by Szlachcic et al. (1985) patients were followed for 12 months after obtaining a measurement of exercise capacity assessed during upright cycle ergometry. After 12 months patients with a $VO_{2Peak} < 10$ $ml.kg^{-1}.min^{-1}$ had significantly higher mortality compared with patients with a $VO_{2Peak} > 10$ $ml.kg^{-1}.min^{-1}$. There are several more recent studies that continue to show a direct

relationship between exercise capacity and survival in heart failure (Bittner et al., 1993; Cleland et al., 1987; Cohn & Rector, 1988; Likoff et al., 1987; Mancini et al., 1991; Parameshwar et al., 1992; Roul et al., 1994). It appears that this relationship is independent of cardiac function, as most studies indicate that even when LVEF is similar those patients with a $VO_{2peak} < 14$ ml.kg^{-1}min^{-1} have a significantly worse prognosis than those with a VO_{2peak}>14 ml.kg^{-1}.min^{-1}.

In the present study the mean absolute VO_{2peak} (1139 $\pm$ 123 ml.min^{-1}) and relative VO_{2peak} (11.86 $\pm$ 3.52 ml.kg^{-1}.min^{-1}) were significantly lower in the heart failure patients compared to the age-matched healthy individuals (2542 $\pm$ 156 ml.min^{-1}; and 30.57 $\pm$ 2.72 ml.kg^{-1}.min^{-1}). The values for exercise capacity in this study are similar to those reported by Szlachcic et al. (1985), Cleland et al. (1987), Likoff et al. (1987), Cohn & Rector (1988), and Roul et al. (1994) indicating a severely impaired exercise capacity. Furthermore, the pretraining exercise capacity (TR: 1176 $\pm$ 370 ml.min^{-1}, 12.15 $\pm$ 3.48 ml.kg^{-1}.min^{-1}) for this group of patients was also similar to the pretraining values reported by Coats et al. (1990) and Adamopoulos et al. (1992). On the other hand the pretraining exercise capacity for this group of patients was slightly lower than those reported by the earlier studies of Sullivan et al. (1988) and Arvan et al. (1988). However, both those studies included several NYHA class I patients. The inclusion of these patients may have increased the average values for exercise capacity. In summary, as is generally observed, the exercise capacity and tolerance, in this subgroup of heart failure patients, was markedly impaired in all patients with an average $VO_{2peak} < 14$ ml.kg^{-1}.min^{-1}. This suggests that this group of patients has a rather ominous prognosis. In fact, in a recent

follow-up of the patients who participated in the acute exercise experiment, it was found that 6 patients had since died confirming the grave prognosis associated with this disease.

One of the primary objectives of the second part of this study was to determine the efficacy of a 16 week exercise training program on exercise tolerance and capacity in patients with heart failure. The results clearly showed that exercise tolerance, as defined by exercise time, and exercise capacity, defined by VO_{2peak}, improved significantly in those patients randomized to the exercise training program compared to pretraining values and the non-training heart failure group. The magnitude of the improvement in exercise tolerance and capacity compared to pretraining values were ~31% and ~24%, respectively, whereas the patients in the non-training group showed no significant change following the 16 week trial.

The magnitude of the improvement in exercise capacity and tolerance in this study are similar to those observed by Sullivan et al. (1988), Jette et al. (1991), and Coats et al. (1990, 1992). The exercise training program in the present study was similar in design to the study by Sullivan et al. (1988) and consisted mainly of walking, with an occasional exercise session on a stationary cycle and/or stair stepper. Sullivan et al. (1988) implemented a 16 week program which included a series of exercise modalities, including: stationary cycling, walking, and stair climbing. The relative increase in VO_{2peak} in Sullivan's study was approximately 23%. However, it should be noted that Sullivan's trial was a non-randomized exercise trial, and included several patients who were NYHA class I patients.

In a more recent trial, a randomized cross-over design was used by Coats et al. (1990, 1992). During the first trial, 11 patients with heart failure, secondary to ischemic heart disease performed 8 weeks of home-based exercise training followed by 8 weeks of "avoidance" of physical exertion (Coats et al., 1990). Exercise consisted of 5 sessions per week on a stationary cycle at an intensity of 60-80% of the pretraining HR_{peak}. Exercise tolerance and capacity increased approximately 25% during the training phase in this study. A similar improvement in exercise capacity was observed following the second trial involving 17 patients with heart failure secondary to ischemic heart disease (Coats et al., 1992). In another randomized trial which only lasted 4 weeks, Jette et al. (1988) reported an improved exercise capacity of approximately 21%. An interesting note to Jette et al. (1988) was that the improved exercise capacity was only evident in those patients with a pretraining ejection fraction < 30%. In the present study the pretraining ejection fraction range was from 18% to 40% and an improvement in exercise tolerance and capacity was noted in all patients randomized to the exercise training group.

Thus, the present study confirms previous data that exercise training can improve exercise capacity and tolerance in patients with heart failure. Importantly, this study is the first randomized trial of this length to report the beneficial role of exercise training on exercise capacity and tolerance. There are several factors that may have contributed to the observed changes in exercise tolerance and capacity. These factors are discussed in the subsequent sections of this chapter.

Doppler echocardiography is the most direct and theoretically most accurate echocardiographic technique for assessing blood flow (Feigenbaum, 1994). The Doppler signal assesses blood velocity, which when combined with the cross-sectional area of the orifice or vessel through which the blood flows provides the basis for quantifying blood flow. There are numerous studies that have demonstrated the feasibility, reproducibility and validity of using the Doppler techniques for measuring blood flow (Christie et al., 1987; Dittman et al., 1987; Nicolosi et al., 1988; Segal et al., 1989). However, despite these studies, many problems remain which complicates interpretation of the data obtained from the Doppler technique. Therefore, prior to discussion of the findings of the present study, several of the known limitations associated with the Doppler approach will be outlined.

To determine blood flow from the Doppler signal one needs to know the average velocity within a vessel. Ideally, one would prefer that one sampling velocity would indicate the average flow within the vessel. This would be the case if the flow through the vessel is uniform, i.e. the velocity of flow in the center of the vessel equals the velocity of flow near the edges of the vessel. However, in reality blood velocity through a vessel is hardly ever uniform. In fact, the blood flow profile is very much a function of the size, shape and length of the vessel. As a result of these limitations, blood flow measurements in the present study were obtained from the aortic root, as it has been

shown that the blood flow profile obtained at a large orifice is much more uniform (Rai & Shah, 1995).

Accurate assessment of the cross-sectional area of the orifice through which the blood flows has proved to be one of the most difficult aspects of Doppler echocardiography (Dittman et al., 1987). As a result, most investigators derive the cross-sectional area from the diameter of the orifice or blood vessel. However, in converting the diameter to area one must square the diameter. Thus, any small error in the measurement of the diameter of the vessel may have a significant impact on the estimated blood flow. To minimize the error associated with measuring the aortic root dimensions, all analyses were performed by one investigator with many years of clinical experience in echocardiography.

Another limitation of the Doppler technique concerns the location of the cross-sectional area in relation to the recording of the Doppler signal. In fact, it is near impossible to know exactly where the Doppler sample is located. In the present study, the location of the Doppler sample with regard to the aortic root is further complicated as a result of a change in body position (supine to upright), and an attempt to obtain the measure during exercise. For the present study it was assumed that the aortic root dimensions were not altered from a supine to upright position, or rest to exercise transition. This assumption may not be totally accurate because some evidence suggests that the vessel does change in size depending on the amount of blood flowing through it (Rai & Shah, 1995). However, in the present study there was no indication that the aortic root dimensions changed from supine to standing, or during exercise.

Thus, despite the apparent limitations of the Doppler technique, it is thought that the measurements of aortic flow are useful in describing the directional changes in cardiac output. Furthermore, the Doppler recording of ascending aortic blood flow can also be used to evaluate left ventricular function, as peak velocity and rate of acceleration may be related to the vigor (contractility) with which the left ventricle contracts.

During exercise, an increase in cardiac output is accomplished by increases in both heart rate and stroke volume (Astrand et al., 1964; Chapman et al. 1960). However, the precise mechanism by which stroke volume increases during upright exercise still remains controversial (Higginbotham et al., 1986; Spina et al., 1992). It is postulated that at low levels of exercise, an increase in left ventricular filling pressure, and end-diastolic volume are important determinants of the stroke volume response through the Frank-Starling mechanism (Chapman et al. 1960; Christie et al., 1987; Higginbotham et al., 1986; Spina et al., 1992). In contrast, at higher intensities of work, exercise tachycardia is often accompanied by a decrease in end-diastolic volume despite a progressive increase in filling pressure, so that the stroke volume must be maintained by a decrease in end-systolic volume (Higginbotham et al., 1986). It is thought that the decrease in end-systolic volume is a result of an increase in myocardial contractility.

In the present study, the pattern of stroke volume and cardiac output were evaluated, with Doppler echocardiography, at five different intensities (1) supine rest, (2) standing rest, (3) 25% of HR_{peak}, (4) 50% of HR_{peak}, and (5) 75% of HR_{peak}. The average supine resting stroke volume was estimated at 79$\pm$20 ml, and cardiac output estimated at 6.54 $\pm$ 1.93 $L.min^{-1}$. Upon standing there was a significant decrease (37%) in the

estimated stroke volume and despite a small increase in heart rate, there was a significant reduction (31%) in the estimated cardiac output. Although, this study is the first to present this finding in patients with heart failure, a similar observation was made by Higginbotham et al. (1986) in healthy adults. In that study a 28% reduction in the stroke volume index was noted going from a supine to sitting position as assessed by radionuclide angiography. In contrast, the cardiac index only fell 16% in healthy adults, compared to 31% in the present study. Although, this difference should be interpreted with caution, it could possibly reflect an impaired baroreflex and decreased capacity to respond to postural changes in heart failure (Dibner-Dunlap et al., 1992; Ellenbogen et al., 1989; Ferguson et al., 1984, 1992; Thames et al., 1993). On the other hand, the change in posture could have resulted in a small change in the aortic diameter which would affect the calculation of stroke volume. Furthermore, a small shift in the position of the aorta in reference to the ultrasound beam could also have affected the stroke volume calculations. Despite, these potential technical difficulties, the consistent decrease in stroke volume and cardiac output from supine rest to standing rest, for all patients suggests a significant and real change in hemodynamics in heart failure.

The pattern of stroke volume during exercise was characterized by a significant (46%) increase at 25% of HR_{peak}, compared to standing pre-exercise values, followed by a gradual decline in stroke volume at 50% and 75% of HR_{peak}. In contrast, cardiac output showed a linear increase with exercise intensity compared to standing pre-exercise values. Thus, it appears that the increase in cardiac output is mediated by both an increase in stroke volume and heart rate at 25%HR_{peak}. However, at 50% and 75% of HR_{peak} the

increase in cardiac output is solely dependent on the increase in heart rate, since stroke volume was shown to decline.

Furthermore, the magnitude of the increase in cardiac output in heart failure appears to be significantly blunted at all exercise intensities compared to healthy adults. For example, in a study by Christie et al. (1987) in healthy adults the percent increase in cardiac output compared to resting values was 125% at 40% of VO_{2peak}, 167% at 60% of VO_{2peak}, 233% at 80% of VO_{2peak}, and 250% at VO_{2peak}. In contrast, in the present study the percent increase in cardiac output from rest was 47% at 25% of HR_{peak}, 61% at 50% of HR_{peak}, and 73% at 75% of HR_{peak}. Although, the intensities are not exactly the same compared to Christie et al. (1987), these data certainly reflect a blunted cardiac output response to exercise in heart failure. This finding confirms previous studies which have also reported a narrowing of the cardiac output reserve capacity with exercise in patients with heart failure (Cohen-Solal et al., 1994; Franciosa et al., 1979, 1984; Higginbotham et al., 1987; Sullivan et al., 1988; Weber et al., 1982, 1985; Wilson et al., 1984). The unique finding of this study is the evaluation of cardiac output during walking. This may provide the clinician with valuable clinical information about how patients with heart failure respond during an activity which is performed on a daily basis.

In summary, the present study indicated that the cardiac output response to an acute bout of exercise is blunted in patients with heart failure. This suggests that patients with heart failure have a narrower cardiac output reserve capacity than age-matched normals. The inability to adequately raise cardiac output during exercise is certain to play a significant role in the exercise intolerance observed in these patients, as previously

shown by several investigators (Bruce et al., 1973; Cohen-Solal et al., 1994; Francis et al., 1982a; Higginbotham et al., 1983; Sullivan et al., 1989; Szlachcic et al., 1985; Weber et al., 1982, 1985).

A disappointment of the present study was the inability to adequately evaluate cardiac function following exercise training. The use of Doppler echocardiography during the exercise condition was significantly affected by technical difficulties and the small number of patients in whom adequate cardiac images and blood flow assessments were collected. Future studies should consider the use of more traditional exercise modalities to evaluate cardiac function, such as upright cycling, and or a semi-recumbent position. Yet, it is important to continue to explore ways to better assess cardiac function during walking, as this continues to be the primary activity for most patients.

The heart rate and blood pressure response to the SL-GXT further indicated the decreased reserve capacity in patients with heart failure. For example, the chronotropic reserve for heart failure was only 54 ± 8 beats, compared to 82 ± 11 beats for the age-matched controls. Clearly the inability to raise the heart rate similarly to controls during a graded exercise test will have an impact on the cardiac output response during exercise. Furthermore, the reduced chronotropic reserve is even more significant since the increase in cardiac output in heart failure patient at higher intensities of exercise, appeared to be largely dependent on an increase in heart rate, since stroke volume was shown to decline. A similar observation was noted for systolic blood pressure, rate pressure product, and O_2pulse. In general, patients with heart failure demonstrated a lower systolic blood pressure, rate pressure product, and O_2pulse at peak exercise, compared to healthy

controls. These findings are consistent with those of Franciosa et al., 1984; Weber et al., 1982, 1985; Sullivan et al., 1989; Wilson & Mancini, 1993 and Cohen-Solal et al., 1994. Although the mechanism(s) responsible for the reduction in hemodynamic reserve capacity in patients with heart failure may be linked to, abnormal reflex control and down-regulation or decreased responsiveness of beta-receptors, it may also reflect the pharmacotherapy of the patient. Irrespective, the exercise response in heart failure in this study was characterized by a narrowing of the reserve capacity of several hemodynamic variables including (1) heart rate, (2) systolic blood pressure, (3) rate pressure product, and (4) O_2pulse. It is thought that the impaired reserve capacity contributed to the exercise intolerance in these patients, as suggested by several other investigators (Colucci et al., 1989; Feldman et al., 1988; Hammond et al., 1985; Hanson, 1994; Higginbotham et al., 1983; Jondeau et al., 1992; Weber et al., 1982).

Exercise training resulted in a small widening of the hemodynamic reserve capacity in patients with heart failure. The chronotropic reserve increased from 55 ± 10 to 64 ± 9 beats, and the peak rate pressure product from 211 ± 53 to 238 ± 65. However, neither the increased chronotropic reserve or peak rate pressure product achieved statistical significance. These findings are similar to Sullivan (1988), although in that study the increase in chronotropic reserve was due to a reduction in resting heart rate after training, whereas in the present study the increase was also due to a non-statistical increase in HR_{peak} following training. In contrast the O_2pulse_{peak} in the present study did significantly increase from 9.38 ± 2.14 to 11.23 ± 2.04 ml.beat^{-1} possibly indicating improved cardiopulmonary function.

In summary, exercise training appears to result in a slight widening of the reserve capacity in patients with heart failure. Clinically, this could result in the patient performing more activities of daily living at a lower percent of the reserve capacity which could reduce the amount of fatigue associated with physical exertion.

Circulatory Responses to Exercise in Heart Failure

Plasma Volume Changes with Exercise in Heart Failure

Several of the adaptations occurring in heart failure influence fluid regulation, vascular reactivity and permeability. It is possible that the alterations in fluid regulation in heart failure contributes to exercise intolerance, shortness of breath, and chronic fatigue secondary to extravascular edema in skeletal muscle and/or the pulmonary system. As previously described vascular wall integrity may be compromised in heart failure due to neuroendocrine-induced alterations in vasomotor tone, increases in arterial wall sodium and water content, increases in edema-induced vascular compression, and changes in vascular wall structure and function (Derman et al., 1995; Drexler et al., 1991; Sinoway et al., 1987; Zelis et al., 1991; Zelis & Flaim., 1982). Since vascular permeability may be altered in heart failure, exercise-induced fluid shift kinetics may also be altered. In healthy adults, exercise produces large fluxes of fluid out of the vascular bed into extravascular compartments (Convertino et al., 1980, 1981; Greenleaf et al., 1979; Kjellmer, 1964; Lundvall et al., 1972; Miles et al., 1983; Senay et al., 1980; Sjogaard et al., 1982; VanBeaumont et al., 1982; Wilkerson et al., 1977). This exercise-induced fluid shift is primarily dependent upon factors influencing capillary exchange dynamics (Landis, 1927; Starling, 1896). They include transcapillary hydrostatic and

colloid osmotic pressures, plasma and interstitial osmolality, and vascular permeability. It has been suggested that increased osmolality during exercise (Greenleaf et al., 1979; Lundvall et al., 1972), elevation in capillary hydrostatic pressure, and increased capillary surface area (Sjogaard et al., 1982; Mohsenin et al., 1984) are primarily responsible for fluid translocation during exercise. In a reciprocal manner, plasma colloid osmotic pressure and interstitial fluid pressure become increasingly important in opposing intra to extravascular plasma volume shifts during maximal exercise (Mohsenin et al., 1984). Alterations influencing vascular permeability may affect fluid translocation during exercise in patients with heart failure. Understanding the pattern of fluid translocation during exercise in heart failure may be clinically relevant because it could have an impact on pharmacokinetics and concentrations.

This study is the first to report significant hemoconcentration during exercise in patients with heart failure. However, the hemoconcentration reported in this study is similar to that reported for healthy adults at VO_{2peak} suggesting that heart failure patients experience similar plasma shift dynamics during SL-GXT (Convertino et al., 1980, 1981; Galbo et al., 1975; Senay et al., 1980; VanBeaumont et al., 1972; 1981; Wilkerson et al., 1977). Dependent upon a subject's training status and exercise modality, plasma volume decreases in a linear fashion and is inversely related to exercise intensity (Senay et al., 1985). Plasma volume shifts in healthy adults are approximately 2-4% at 40% VO_{2peak}, 7-10% at 70% VO_{2peak}, and 12-16% at VO_{2peak} (Senay et al., 1985). The 10.55% (mean) decrease in plasma volume at VO_{2peak} observed in these patients is similar to the 12-16% decrease at VO_{2peak} reported for healthy adults. Thus, the exercise-induced plasma

volume shift appears to be dependent on exercise intensity (VO_{2peak}) and independent of exercise capacity (Galbo et al., 1975; Vanbeaumont et al., 1981). The small difference between the relative plasma volume shift observed in this study (10.55%) and those reported for healthy adults (12-16%) may be attributed to the fact that heart failure patients are more likely to terminate the SL-GXT prematurely due to onset of symptoms and/or anxiety related to high intensity exercise.

It is difficult to compare the findings of this study to prior reports due to methodological differences, as well as differences in data collection techniques. Hagan et al. (1980) concluded that, whenever plasma volume changes are measured, body position, duration of time in that position, and specific time of blood sampling are important factors. In several studies, subject positioning during blood sampling and time between postural changes and when blood samples were drawn varied or were inconsistent or unreported (Costill et al., 1974; Senay et al., 1980; Vanbeaumont et al., 1981; Wilkerson et al., 1977). Blood samples were collected at either unspecified times and/or with the subject resting in either supine, seated, or standing position. Following or during exercise blood samples were again obtained with the subject in a posture unrelated to the initial posture of the subject or without regard to time in that posture. In the present study, we attempted to minimize the hematologic alterations associated with postural changes by allowing 20 minutes between movement from a supine to standing position, and by standardizing patient posture (standing) as well as the timing of blood sampling relative to the exercise session. Other factors are also known to influence plasma volume during exercise. They include modality, intensity, duration, ambient

temperature and humidity, gender, training state, and hydration state (Senay et al. 1985). The protocol in the present study was standardized in an effort to minimize the effect of these factors.

Patients with heart failure exhibit impaired vasodilatory capacity which can be attributed to many factors. Despite pharmacological intervention (e.g. digoxin, diuretics, ACE-inhibitors), edema, altered vessel morphometry, and impaired vascular reactivity are found in heart failure (Derman et al., 1995; Drexler et al., 1991; Sinoway et al., 1987; Zelis et al., 1991; Zelis & Flaim., 1982). Drexler et al. (1991) describe the neurohumoral factors that increase systemic vasoconstriction and decrease vascular reactivity and, thus may alter vascular permeability. Interestingly, these neuroendocrine responses are also found during acute high intensity exercise in healthy adults and include elevated plasma levels of renin, angiotensin II, aldosterone, arginine vasopressin, and atrial natriuretic peptide (Convertino et al., 1980, 1981, 1983; Freund et al., 1987). Whereas angiotensin II and arginine vasopressin produce vasoconstriction, atrial natriuretic peptide, which is released from the right atrium in response to expanded central blood volume and edema, induces diuresis and natriuresis and relaxes vascular smooth muscle in an attempt to reduce blood volume and MAP (Anand et al., 1989; Casnocha et al., 1987; Lockette, et al., 1990). Chronic high concentrations of atrial natriuretic peptide, as observed in heart failure patients, may attenuate excessive fluid retention but potentially augment edema by increasing vascular permeability to albumin (Lockette et al., 1990; Sheriker et al., 1985). It was hypothesized that the chronic elevation in neurohumoral concentrations (angiotensin II, arginine vasopressin, atrial natriuretic peptide, aldosterone) as well as

other factors (altered vascular morphology, extravascular edema) characteristic in heart failure patients, could have significantly affected fluid shift kinetics during maximal treadmill exercise. However, since plasma volume shifts were similar to those reported for healthy adults, it is unlikely that these factors significantly affected the cumulative Starling forces responsible for fluid shift dynamics.

The potential for differences in fluid shift kinetics could have important implications for designing pharmacological treatment and cardiac rehabilitation programs for heart failure patients. In healthy adults, exercise-induced flow-mediated vasodilatation increases blood flow thereby improving nutrient supply to active muscle and up-regulating metabolic function (Mohsenin et al., 1984). However, although the aqueous portion of plasma may shift to extravascular spaces, the concentration of red blood cells, plasma proteins, neurohormones (i.e. plasma renin activity, arginine vasopressin, atrial natriuretic peptide), and pharmacological agents would be expected to increase substantially during exercise in healthy subjects (Hartley et al., 1972; Hurwitz et al., 1983; Senay et al., 1985; Van Baak et al., 1990, 1992). Although changes in drug concentrations were not reported in the present study, the fact that corrected hematocrit increased 3.8% and plasma proteins increased 7.03% indicate substantial hemoconcentration. In fact, the substantial rise in neurohumoral concentrations may be partially explained by the hemoconcentration. Only a limited number of studies have evaluated the effect of exercise on the pharmacokinetics of drugs. From these studies, it is clear that exercise does influence the pharmacokinetics of propranolol (Henry et al., 1981; Hurwitz et al., 1983; Van Baak et al., 1992), verapamil (Van Baak et al., 1992), and

other cardiac active medications (Van Baak et al., 1990). Recognizing the increasing acceptance of cardiac rehabilitation programs for patients with heart failure, exercise-induced increases in plasma drug concentrations as well as endogenous neurohormones could theoretically alter drug efficacy and should be considered when prescribing pharmacotherapy and exercise. Further research is clearly warranted regarding this matter.

In summary, these results show that an acute bout of maximal exercise in heart failure patients causes a plasma volume shift from the intra to extravascular compartment averaging 10.55%. The direction and magnitude of this shift appear similar to data reported for healthy adults. The plasma volume shift appears to be related to peak exercise intensity, is independent of peak exercise capacity and remains unchanged following training. Recognizing that hemoconcentration occurs during exercise, the results of the present study may have implications in understanding pharmacokinetics and prescribing rehabilitative exercise programs for heart failure patients (Feigenbaum et al., 1996).

Neurohumoral Responses to Exercise

There is evidence that exercise intolerance in heart failure is linked to neurohumoral activation (Drexler et al., 1991; Frances et al., 1982a, 1982b, 1984; Kirlin et al., 1986; Packer et al., 1988). Frances et al. (1982a) reported that basal supine plasma norepinephrine was inversely related to exercise capacity in patients with heart failure. Others have demonstrated an increased activity in the renin-angiotensin-aldosterone system (Curtiss et al., 1978; Merrill et al., 1946), arginine vasopressin (Creager et al.,

1986; Goldsmith et al., 1983, 1986), atrial natriuretic peptide (Benedict et al., 1993; Donckier et al., 1991; Keller et al., 1988; Riegger et al., 1986), and endothelin (Krum et al., 1995; Stewart et al., 1990). Although, the mechanism through which these neurohumoral factors impact exercise capacity is presently not well understood, it is postulated that the combined effect of these factors result in an increase in vascular resistance and reduced skeletal muscle blood flow (LeJemtel, 1986; Zelis et al., 1988). It is thought that reduced skeletal muscle blood flow during exercise contributes to the exercise intolerance in heart failure.

In the present study plasma concentration of angiotensin II, arginine vasopressin, aldosterone, and α-atrial natriuretic peptide were all elevated compared to a healthy control group previously studied in this laboratory using similar standardization techniques and assay procedures. This suggests that despite standard pharmacotherapy, including ACE-inhibitors, diuretics and digitalis, pre-exercise neurohumoral levels in this group of heart failure patients remained high compared to healthy adults. Interestingly, when the data of the present study is compared to other studies involving patients with heart failure, there appears to be some discrepancy. For example, the mean rest supine venous plasma atrial natriuretic peptide and arginine vasopressin from the SOLVD trial were 114 [range 54 to 225] $pg \cdot ml^{-1}$ and 2.4 [range 1.9 to 3.5] $pg \cdot ml^{-1}$, respectively in 89 patients with an LVEF < 45% (Benedict et al., 1993). The mean pre-exercise values for atrial natriuretic peptide and arginine vasopressin in this study are 68% less and 150% higher than those in the SOLVD-trial, respectively. The reason for the different arginine vasopressin and atrial natriuretic peptide in this study compared to the SOLVD trial is not

completely clear, but may be secondary to laboratory differences in the radioimmunoassay procedures, an anticipatory effect prior to physical exertion, and/or obtaining the blood sample in an upright position. The baseline plasma angiotensin II, aldosterone, and atrial natriuretic peptide in the CONSENSUS-trial were 72.2, 1383, and 463 $pg \cdot ml^{-1}$, respectively, which is significantly higher than presented in this study. However, it is important to note that the patients included in the CONSENSUS-trial were all patients with a NYHA class IV, and thus severe heart failure. Thus, it appears that the inter-study differences in neurohumoral concentrations at rest may be affected by several factors including (1) severity, duration and etiology of heart failure, (2) method of blood sampling, e.g. arterial versus venous, supine versus standing, fasting versus non-fasting, (3) pharmacotherapy, and (4) inter-laboratory radio-immunoassay variability.

An acute bout of exercise resulted in a significant increase in angiotensin II, arginine vasopressin, and atrial natriuretic peptide in this study. The percent change from pre-exercise for angiotensin II was approximately 175%. The percent change from pre to peak exercise is higher in this study compared to a similar study by Sigurdsson et al. (1994). In the study by Sigurdsson et al. (1994), 27 patients on diuretic therapy and ACE-inhibition (i.e. Ramipril) performed an upright cycle exercise test to volitional fatigue or significant clinical symptoms. Exercise resulted in an average increase of 100% in angiotensin II. The difference between studies may be due to the manner in which blood samples were collected and the choice in exercise modality. For example, in Sigurdsson's study pre-exercise blood samples were obtained in the supine position and peak exercise samples in a sitting position. In the present study blood samples were obtained in the

same position, recognizing that postural shifts may influence hematologic variables as described by several authors (Costill et al., 1974; Hagan et al., 1980; Senay et al., 1980).

In the present study, the percent change from pre to peak exercise for atrial natriuretic peptide was approximately 60%. The percent change with exercise is slightly higher than those reported by Sigurdsson et al. (1994) but similar to those reported by Nicholls et al. (1992). The discrepancy between Sigurdsson et al. (1994) and the present study may again be related to the methodological differences regarding blood sampling and exercise testing. In the study by Nicholls et al. (1992) 28 individuals with heart failure, secondary to ischemic heart disease, also performed a graded exercise test on a treadmill, resulting in a 70% increase in venous plasma levels of atrial natriuretic peptide. The small difference between studies may be due to a correction for plasma volume shifts in the present study.

A larger difference in the exercise response between studies was observed for aldosterone. Whereas in the present study the percent change from pre to peak exercise for plasma aldosterone was only 11.50%, Nicholls et al. (1992) and Sigurdsson et al. (1994) reported a 50% change at peak exercise. It is unclear what could be the cause of such a different neurohumoral response for aldosterone, yet similar change for atrial natriuretic peptide between studies. Clearly, further studies are warranted to determine the exercise changes in neurohumoral factors.

One of the unique findings of this study is an apparent reduction in pre-exercise neurohumoral concentrations. A consistent reduction in angiotensin II, aldosterone, arginine vasopressin, and atrial natriuretic peptide was observed in those patients

randomized to the exercise training group. This study is the first to report a change in the fluid-regulatory hormones in patients with heart failure following training. Coats et al. (1992) reported improved autonomic function in patients with heart failure following 8 weeks of exercise training. In the study by Coats et al. (1992), autonomic function was measured using power spectral analysis of RR interval variability, and norepinephrine kinetics. Exercise training resulted in increased heart rate variability, and a significant reduction in whole-body norepinephrine spill-over, suggesting a reduced sympathetic nervous system activity and/or restoration of the baroreflex. In this study, catecholamine samples have been obtained. However, as of yet these samples have not been analyzed until further funding has been made available.

Several "training-adaptations" in the present study could have contributed to the reduced pre-exercise neurohumoral values. For example, the reduction in pre-exercise plasma concentrations of the fluid-regulatory hormones may reflect a decreased sympathetic stimulus to the kidneys, thereby reducing the renin-angiotensin-aldosterone activity. Furthermore, exercise training could possibly play a role in restoring the baroreceptor reflex. Finally, subjects randomized to the exercise group may have developed better muscle tone, allowing for improved venous return, and maintenance of right atrial pressures in the upright position, or are in fact standing at a lower exercise-intensity compared to pretraining values. Interestingly, the peak exercise neurohumoral concentrations were not altered following the training period. Yet, due to the decreased pre-exercise fluid-regulatory hormone values, it appears that there is a slight widening of the neurohumoral reserve capacity following exercise training in heart failure.

Skeletal Muscle Metabolic Responses to Exercise in Heart Failure

The controlled use of energy to maintain homeostasis and perform work is a basic property of all cells (Balaban, 1990). As a result an intricate multitiered control system exists between the rate of energy conversion (ATP production) and expenditure. Several potential cytosolic "sensors" have been proposed as regulators of intermediary metabolism and include (1) ATP hydrolysis products, (2) substrate delivery to the electron transport chain, and (3) oxygen delivery.

During a rest-to-work transition the rise in VO_2 is generally slow, whereas glycolysis is rapidly activated as an ATP source (Connett, 1987). Although, the mechanism involved in the initial glycolytic recruitment is not fully understood, it is thought to be the result of cytosolic alkalization secondary to a shift in the creatine kinase equilibrium position. In the present study, the rest-to-work transition was always characterized by a slight but statistically significant increase in muscle pH. This initial period of alkalization is thought to be a major regulatory factor in the early burst of glycolysis during the rest to work transition period (Connett, 1987). The alkaline shift in cytosolic pH has been proposed to play a major role in promoting conversion of phosphorylase b to phosphorylase a, and serves as an activating signal for phosphofructokinase (Danforth et al., 1964). The combination of these factors are thought to increase the rate of glycogen breakdown, glycolysis and eventually the production of ATP.

However, as the demand for energy continues, the ATP production from anaerobic metabolic pathways becomes inadequate and muscle pH begins to fall. It is

hypothesized that the increase in the cytosolic concentration of ATP hydrolysis products (ADP and Pi) then serve an important role in the regulation of oxidative phosphorylation. In the present study, the ATP/ADP*Pi ratio dropped significantly after the first 30 sec to 60 sec of exercise. The decrease in ATP/ADP*Pi represents the signal to the mitochondria to increase energy production through oxidative metabolism. Despite the ATP/ADP*Pi signal, the exercise response was characterized by a gradual fall in muscle pH. The source of the fall in pH is thought to be an increase in several metabolic enzymatic reactions (e.g. citrate synthetase and malate dehydrogenase) which involve the production of protons. An important function of this gradual fall in pH is a reduction of those factors responsible for the initial inhibition of mitochondrial function (Connett, 1987). In summary, the initial rest-to-work transition glycolysis is rapidly activated as an ATP source. Continued cellular demand results in an increased reliance on oxidative phosphorylation to maintain ATP levels.

The Pi/PCr ratio has been proposed as a marker of oxidative metabolism. This is because Pi/PCr, through the creatine kinase reaction, reflects the ADP in muscle. It has been hypothesized that ADP serves as a major regulator of mitochondrial respiration in mammalian skeletal muscle. Chance et al. (1981, 1985, and 1986) were the first to determine that the relationship between work rate and "energy cost", expressed as Pi/PCr, was a reflection of mitochondrial function. Because Pi/PCr can be utilized to estimate intracellular ADP, the dynamics of ADP control of oxidative phosphorylation can be calculated, and the oxidative ability of muscle estimated. Several studies have demonstrated a much greater rise in Pi/PCr at any given relative workload in untrained

compared to trained individuals (Kent-Braun et al., 1995; McCully et al., 1989) and young versus old (McCully et al., 1993), indicating a decreased ability to keep pace with energy demands by means of oxidative phosphorylation. Subsequent studies have shown that endurance training increases the capacity for oxidative phosphorylation, as measured by a decrease in the Pi/PCr ratio at any given relative workload (Kent-Braun, 1990; McCully et al., 1991; Minotti et al., 1990). Thus, the Pi/PCr ratio appears to be an acceptable and sensitive marker to evaluate changes in skeletal muscle oxidative metabolism.

In the present study, the Pi/PCr_{prex} ratio was not significantly different between age-matched controls and heart failure patients, prior to low and high intensity exercise. In contrast, with the onset of low and high intensity exercise the rise in Pi/PCr was always more pronounced in heart failure reflecting an impairment in oxidative metabolism and a greater reliance on glycolytic pathways to meet energy demands. The greater rise in Pi/PCr during exercise in heart failure has also been reported by several other investigators, using forearm flexor and gastrocnemius muscle groups, and similar experimental protocols. The greater rise in the Pi/PCr ratio during the low intensity work load in heart failure compared to controls, in this study were similar to those found by Wilson et al. (1985), Wiener et al. (1986) and Minotti et al. (1990). Wilson et al. (1985) and Wiener et al. (1986) used a forearm-exercise protocol and evaluated forearm blood flow and skeletal muscle energetics at three submaximal workloads. The major finding of these studies was that forearm muscle metabolism was altered during exercise, despite comparable blood flow in patients with heart failure versus healthy controls. Minotti et

al. (1990) also determined the effect of handgrip exercise on forearm muscle energetics and noted a substantial rise in Pi/PCr at submaximal workloads compared to age-matched controls suggesting a decreased ability to meet energy demands through oxidative metabolic pathways. The data from the present study further extend the findings by Wilson et al. (1985), Wiener et al. (1986), and Minotti et al. (1990) demonstrating impaired oxidative metabolism at a low intensity exercise work load in the medial head of the gastrocnemius muscle in patients with heart failure. Other investigators, using ramp protocols have also reported impaired oxidative metabolism in the calf muscle of heart failure patients (Arnolda et al., 1990; Chati et al., 1994; Mancini et al., 1988, 1989, 1992). Generally, in these studies heart failure patients achieve a lower maximum workload with lower muscle pH and greater oxidative stress as indicated by Pi/PCr or PCr/(PCr + Pi). In the present study, the high intensity exercise bout may have been somewhat similar to a ramp protocol. The high intensity exercise was specifically designed to determine the skeletal muscle metabolic responses during a fatiguing bout of exercise. The results demonstrated a greater rise in Pi/PCr in heart failure compared to control. In addition, patients with heart failure suffered the early onset of fatigue, as defined by time to volitional exhaustion.

Although the greater rise in the Pi/PCr ratio is thought to reflect a change in oxidative metabolism, several other factors could potentially explain the increased Pi/PCr_{ex}. These factors include changes in muscle mass or strength, recruitment pattern, and blood flow, in addition to variations in radiofrequency coil placement and limb placement.

A decrease in muscle mass or strength could result in an increase in the Pi/PCr_{ex} during submaximal exercise because the sampled tissue would be working at a higher relative exercise intensity (Mancini et al., 1992). However, in the present study measures of body composition (body weight, skinfold, and calf circumference) were similar between heart failure and healthy controls suggesting that muscle mass was not a significant factor. Certainly, the crude measure of body composition may not be sensitive enough to detect any local muscle atrophy. Yet, since measures of force were not different between groups it seems unlikely that muscle atrophy in heart failure could totally explain the observed increase in Pi/PCr_{ex}.

Another mechanism that could explain a higher Pi/PCr_{ex} could be a different recruitment pattern. Differences in muscle recruitment have been reported in highly conditioned athletes. However, the effect of heart failure on motor unit recruitment is currently not well understood. To minimize the neural contributions to changes in Pi/PCr, the in-magnet exercise was performed in the same manner, using the same conditions, and at the same relative workloads for all subjects.

Another variable that could potentially cause a more pronounced increase in Pi/PCr_{ex} is a different blood flow response to the gastrocnemius muscle during exercise. Yet, Wiener et al. (1985), Wilson et al. (1986), and Minotti et al. (1990) have all demonstrated a greater rise in Pi/PCr during forearm exercise in heart failure compared to control, despite a similar blood flow response. Furthermore, Massie et al. (1988) found that the skeletal muscle metabolic responses to exercise in heart failure were still markedly different under ischemic conditions. However, it is possible that in heart failure

an altered blood flow distribution and oxygen delivery to local muscle beds may somehow affect the metabolic responses to exercise. Therefore, a limitation of the present study was the inability to assess limb blood flow during the in-magnet protocols. On the other hand, the low intensity work load and the relative small muscle volume studied were more than likely not significant stimuli to alter blood flow markedly during exercise. It is, therefore, believed that oxygen delivery during our experimental conditions was not rate limiting in skeletal muscle metabolism.

Inconsistent placement of the radiofrequency coil over the muscle sample of interest could result in evaluation of different regions of muscle. Such variation could alter the Pi/PCr response to exercise. To facilitate collecting data from the same area, great care was taken to ensure proper positioning of the radiofrequency coil and of the leg in the magnet. The thickest portion of the medial head of the gastrocnemius was identified and marked by the same investigator on each test. The distance of the mark on the medial head of the gastrocnemius to the lateral epicondyle of the tibia was recorded for each patient. Placement of the radiofrequency coil was directly over the area marked and standardized for each testing period. As a result of these procedures metabolic comparisons are thought to be valid.

In summary, data from the present study suggests that in heart failure oxidative metabolism is impaired with subsequent greater reliance on glycolytic pathways to meet energy demands. The increased reliance on anaerobic glycolysis will result in an increase in Pi and H^+ production, and could be two potential factors involved in the

early onset of skeletal muscle fatigue. Thus, the observed exercise intolerance in heart failure can in part be explained by these skeletal muscle adaptations.

The increase in intracellular Pi and H^+ during muscular work appear to be related to a decrease in contractile tension and subsequently the development of fatigue. However, more recent studies have identified a stronger correlation between the diprotonated form of Pi ($H_2PO_4^-$) and the decline of force and development of fatigue (Boska et al., 1990; Cady et al., 1989; Dawson et al., 1988; McCully et al., 1991; Miller et al., 1988; Weiner et al., 1990; Wilkie et al., 1986; Wilson et al., 1988). A unique finding of this study was that exercise resulted in a dose-dependent increase in $H_2PO_4^-$. The magnitude of the increase was significantly greater in heart failure compared to controls, and appears to be independent of the H^+. Furthermore, perceived exertion was greater for the heart failure patients during low intensity exercise, and exercise tolerance significantly reduced during the high intensity work bout.

Fatigue during activity is a cardinal symptom in patients with heart failure. Traditionally, it was thought that this limitation was the result of inadequate blood flow to exercising muscle (Zelis & Flaim, 1982). As already described, more recently studies have demonstrated that the reduced exercise tolerance is multifactorial including intrinsic skeletal muscle alterations (Drexler et al., 1992; Lipkin et al., 1988; Mancini et al., 1989; Massie et al., 1988; Sullivan et al., 1990). In general, the consequence of these skeletal muscle alterations is a depressed oxidative capacity in exercising muscle of patients with heart failure. It is thought that the reduction in oxidative capacity is secondary to ultrastructural abnormalities of skeletal muscle such as more pronounced atrophy of

muscle fibers classified as Type I, a marked decline in mitochondrial enzymes (Succinate dehydrogenase, Citrate synthase and cytochrome oxidase), and a reduction in mitochondrial volume and density (Drexler et al., 1992; Lipkin et al., 1988; Mancini et al., 1989; Massie et al., 1988; Sullivan et al., 1990).

Interestingly, the majority of the above-mentioned studies have focused on identifying the mechanism(s) related to the marked impaired exercise capacity, as defined by VO_{2peak}. Yet, few studies have focused on the etiology of skeletal muscle fatigue in heart failure during short periods of activity. Such studies are important in understanding the symptoms reported by heart failure patients whilst performing repeated tasks such as dressing, cooking, and/or house cleaning.

A number of intramuscular metabolic factors have been linked to fatigue (Fitts, 1994). These factors include (1) an accumulation of hydrogen ions, (2) accumulation of Pi, (3) depletion of PCr reservoirs, and (4) ATP depletion. The proposed mechanisms by which H^+ ion accumulation are thought to contribute to muscle fatigue include (1) a reduction of cross-bridge transition from the low to high force state, (2) enhanced Ca^{2+} binding to the sarcoplasmic reticulum, (3) increased requirement for Ca^{2+}, and (4) through inhibition of glycolysis (Fabiato et al., 1978; Metzger, 1990; Nakamura et al., 1972; Spriet et al., 1989). Yet, despite this seemingly convincing data, there are studies in patients with certain metabolic deficiencies in which rapid muscular fatigue is evident, even though muscle pH does not fall (Chance et al., 1985; Ross et al., 1981). Other studies have questioned whether the change in pH is sufficient to explain muscle fatigue or have been able to alter the relationship between pH and muscle force under certain

conditions (Baker et al., 1994; DeGroot et al., 1993; Wilson et al., 1988). Thus, although there appears to be a role for H^+ in fatigue it is not necessarily a cause and effect relation (Miller et al., 1988, 1993).

In the present study there was a statistical difference in the pH response during the low intensity workload, suggesting that H^+ ion accumulation could have played a role in the increased perception of work. However, it is doubtful that such a role was significant as the pH did not change much with exercise in either group. On the other hand, the pH response during the high intensity workload was much more pronounced but not statistically different between heart failure and controls. This suggests that the accumulation of H^+ ion was not the primary cause of the muscle fatigue observed in heart failure during the high intensity workload.

In contrast, in this study there was a significant greater rise in Pi during both the low and high intensity workloads in heart failure. A rise in Pi and a decrease in PCr with exercise has been linked to the development of fatigue (Dawson et al., 1988; Miller et al., 1988; Weiner et al., 1990). However, controversy exists regarding the active species of Pi in the etiology of fatigue (Wilkie et al., 1986). Inorganic phosphate exists in either a monoprotonated or diprotonated ($H_2PO_4^-$) form. It is thought that the ratio of monoprotonated to $H_2PO_4^-$ depends on the H^+ (Nosek, 1990). However, increasing the total Pi at a fixed pH will also increase both charged forms. Thus, the greater rise in $H_2PO_4^-$ during exercise in heart failure, is in large due to an increase in Pi rather than H^+ accumulation.

Several studies suggest that it is the acidic form of Pi, $H_2PO_4^-$, that is the causative factor in fatigue (Boska et al., 1990; Cady et al., 1989; Dawson et al., 1988; McCully et al., 1991; Miller et al., 1988; Weiner et al., 1990; Wilkie et al., 1986; Wilson et al., 1988). The present study is the first to demonstrate a marked elevation of $H_2PO_4^-$ during different intensities of exercise and to suggest a link to the clinical manifestations of muscle fatigue in heart failure. The concept that accumulation of $H_2PO_4^-$ is primarily responsible for fatigue was originally proposed by Dawson et al. (1986) who observed a high correlation between the decline in force and the increase in $H_2PO_4^-$. Other investigators have confirmed a close relationship between $H_2PO_4^-$ and force development using a variety of species, muscles, and protocols (Boska et al., 1990; Cady et al., 1989; McCully et al., 1991; Miller et al., 1988; Weiner et al., 1990; Wilkie et al., 1986; Wilson et al., 1988). These studies provide convincing evidence that the relationship between $H_2PO_4^-$ and fatigue is stronger and more consistent than the relationship between H^+ accumulation and fatigue. This is not to say that intracellular pH and total Pi are not important determinants of muscle fatigue, but the single metabolite that seems to correlate most closely with muscular fatigue is the build-up of $H_2PO_4^-$ (Boska et al., 1990; Cady et al., 1989). Thus, examination of $H_2PO_4^-$ is of interest since it integrates changes in two variables, pH and Pi, which appear to have separate and additive effects in decreasing contraction force.

Although, the mechanism whereby $H_2PO_4^-$ causes fatigue is presently not clear it is hypothesized that an increase in Pi, and thus $H_2PO_4^-$, reverses the force-producing step of the cross-bridges (i.e. the release of Pi from the cross-bridge) by shifting the

distribution of cross bridges towards those states with a full complement of bound products (ADP and Pi) (Hibberd et al., 1985). Such a shift would lead to a decrease in the available number of force-producing cross bridges, a reduction in developed tension, and muscular fatigue.

The reason for the marked elevation of $H_2PO_4^-$ in heart failure is also not known, but could be related to impaired oxidative metabolism. The handling of Pi appears to depend on a mitochondrial membrane carrier protein for the transport of Pi into the mitochondria. This carrier protein appears to be specific for the diprotonated form of Pi (Iotti et al., 1991). Several studies have confirmed a significant reduction in mitochondrial volume and density in patients with heart failure (Drexler et al., 1992; Lipkin et al., 1988; Mancini et al., 1989, 1992). Additional studies have shown that specific carrier systems within the mitochondrial membranes are inhibited in heart failure, e.g. the pyruvate dehydrogenase complex (Wargovich et al., 1988), the carnitine translocase system (Opie, 1979; Pepine & Welsch, 1995), and the adenine nucleotide translocase (Opie, 1979). Although, there are no studies in heart failure that have looked at the Pi carrier system, it is reasonable to speculate that a reduction in mitochondrial volume or density and inhibition of carrier systems could alter the handling of high energy phosphates during exercise. Such a condition could alter the handling of Pi and contribute to an increase in the cytosolic $H_2PO_4^-$.

The interpretation of these results are complicated for several reasons. First, the increased perception of work and reduced exercise time might not be solely due to muscle fatigue, but could be caused by other factors such as discomfort associated with impaired

blood flow to the region, shortness of breath, or general anxiety about physical exertion. Although, we can not exclude the potential importance of impaired nutritive flow to muscle, there was no significant difference in symptoms (such as calf pain, shortness of breath, chest pain etc.) reported between the groups. Second, it can be argued that perception of work and exercise time are not sensitive markers of muscle fatigue, although previous research has established the importance of the RPE scale as an indicator of fatigue (Borg, 1982). Nevertheless, performance of a post exercise MVC could have better confirmed muscular fatigue by measuring the loss of contractile function. Third, the medial gastrocnemius muscle is a heterogeneous muscle and different fibers fatigue at different rates. The metabolic changes as measured by ^{31}P NMR, represent changes of all fibers under the coil. It is not known if there are specific fibers which may exhibit more dramatic changes under the conditions imposed (Baker et al., 1992). Heart failure patients generally have a relative greater atrophy of oxidative fibers compared to glycolytic fibers. Fourth, it is certainly recognized that muscular fatigue is a complex and multifactorial process. No single parameter or metabolite is capable of explaining such a complicated process as fatigue (Fitts, 1994).

The clinical implications of these findings are speculative but offer further insight into the etiology of the marked activity intolerance in patients with heart failure. Many essential activities of daily living require relative short bouts of muscular activity. These findings suggest that the marked elevation in $H_2PO_4^-$ during short bouts of exercise may play a significant role in the development of symptoms of fatigue. Additional studies are warranted to further confirm the role of $H_2PO_4^-$ in muscle fatigue and to determine its

relationship to functional ability in patients with heart failure. Future studies should also aim to determine to what degree the skeletal muscle responses in heart failure are inherent to the disease, and whether interventions, such as exercise training, could alter these changes.

Thus, the present findings demonstrate that exercise results in a dose-dependent increase in $H_2PO_4^-$. The magnitude of the increase in $H_2PO_4^-$ was significantly greater in patients with heart failure, and appears to be less dependent on the H^+ and more related to the Pi. The marked increase in $H_2PO_4^-$ in heart failure was associated with a greater perceived exertion during low intensity exercise, and early fatigue during the high intensity work bout. The marked elevation in intramuscular $H_2PO_4^-$ with exercise may contribute to the marked exercise intolerance and symptoms of muscular fatigue exhibited during short duration activities in patients with heart failure.

Another method for comparing oxidative metabolism between heart failure and controls is to evaluate the recovery kinetics of PCr. A major advantage of measuring PCr_{res} is that it is independent of work intensity, muscle mass, and recruitment provided that pH is not markedly different (Mahler et al., 1985; McCully et al., 1991; Meyer, 1988). The use of PCr_{res} (T1/2) to indicate the capacity for mitochondrial oxidative phosphorylation was originally based on biopsy data (Hultman et al., 1981). Resynthesis of PCr in the cytoplasm is catalyzed by creatine kinase. The activity of this enzyme in skeletal muscle is high and the reaction is maintained at or near equilibrium. Thus, it is postulated that the PCr is determined by the other species in the equation: PCr = {[mgATP] * [Creatine] / Keq [mgADP] [H^+]}. Since the concentration of ATP and

creatine do not significantly change during moderate exercise conditions, it follows that the PCr at any time during recovery from exercise must be determined by the cytosolic ADP and pH.

Data from the present study demonstrate that PCr_{res} is significantly prolonged following both low and high intensity in patients with heart failure compared to controls. Although the prolonged PCr_{res} following the low intensity exercise bout could be partially explained due to a statistical significant decrease in muscle pH between heart failure and control, intramuscular pH was similar during the high intensity workload. This suggests that the difference in PCr_{res}, following high intensity exercise, is a function of a different rate of net rephosphorylation of ADP. It is hypothesized that the rephosphorylation of ADP following exercise is dependent on mitochondrial oxidative phosphorylation and is independent of workload and muscle mass (Kent-Braun et al., 1995). Several other investigators have also found the half-time of PCr recovery to be increased in heart failure compared to controls (Chati et al., 1994; Cohen-Solal et al., 1995; Mancini et al., 1988; Massie et al., 1987). On the other hand the half-time for PCr recovery is decreased in athletes (McCully et al., 1993), suggesting that the PCr_{res} is characteristic of the oxidative pathway capacities of the subjects (Cohen-Solal et al., 1995). In the study by Massie et al. (1987), PCr recovery was very slow (PCr_{res} (T1/2) > 2 min) in some patients. However, a 10 to 20% decrease in ATP during exercise could have altered the recovery kinetics in these patients. The PCr time constants (half-times) reported by Mancini et al. (1988) appear to be similar to those reported in the present study, even though the exercise protocol used involved a ramp test. The PCr time constant reported by Mancini

et al. (1988) ranged from 39 sec to 259 sec with a mean of 82 sec for the heart failure patients, compared to 14.8 sec to 51.1 sec for the control subjects. Thus, the changes in the PCr_{res} reported in this study are similar to previously reported values and are thought to reflect impaired oxidative metabolism.

An interesting and unique finding of the present study was a comparison of the relationship between the level of PCr depletion (or change in PCr from pre-exercise) and the PCr recovery slopes between groups. In the control group, it appears that the rate of recovery was inversely related to the change in PCr from pre to end exercise. In other words, the greater the change in PCr during exercise the slower the rate of recovery, and the smaller the change the faster the recovery. This finding is consistent with previous work by Arnold et al. (1984) who noted a slower PCr_{res} following heavy exercise. In contrast, in heart failure the rate of recovery of PCr was only weakly related to the change in PCr from pre to end exercise during low intensity exercise. Furthermore, there was a virtual dissociation of recovery rate and PCr depletion at high intensity exercise. Although the exact explanation for this difference between controls and heart failure is not entirely clear, it may provide a better understanding why patients with heart failure are unable to recover from submaximal efforts and perform regular daily activities.

A prolonged ATP/ADP*Pi half-time in heart failure compared to control may provide yet another index of a metabolic abnormality in skeletal muscle (Balaban, 1990). The rate of oxidative rephosphorylation is dependent on the extra-mitochondrial ADP and Pi. Therefore, the delivery of the ATP hydrolysis products, ADP and Pi, are thought to be excellent feedback signals to oxidative phosphorylation during changes in work,

recovery or ATP-ase activity. The ATP/ADP*Pi model is based on the concept that the majority of the mitochondrial respiratory chain is in near-equilibrium with the cytosolic phosphorylation potential (Stainsby et al., 1990; Wilson et al, 1979,1985). Shifts in any of the equilibrium constituents (i.e. NAD/NADH, ATP/ADP*Pi, Cytochrome c etc.) would result in alterations in cytochrome aa3 redox state, which is the ultimate controller of respiration through the irreversible step in the reduction of molecular oxygen. The present study is the first to suggest that ATP/ADP*Pi recovery kinetics are altered in heart failure. Mean half-times for ATP/ADP*Pi following exercise were consistently higher for heart failure compared to controls. The observed increase in ATP/ADP*Pi half-time recovery kinetics is thought to reflect (1) a decreased movement of ATP hydrolysis products into the mitochondrial matrix, (2) a decrease in mitochondrial volume or density, and/or (3) a decrease in mitochondrial enzyme activity and/or concentration.

A criticism of the ATP/ADP*Pi model is the lack of consistency in the literature that the extra-mitochondrial phosphorylation potential is indeed in equilibrium with the intra-mitochondrial space (Balaban, 1990). Studies from several laboratories have shown that the adenylate translocase is not equilibrating intra and extra mitochondrial ATP and ADP in active mitochondria (Tager et al., 1983). In fact, during episodes of ischemia long-chain acyl CO-A esters impair the activity of the adenylate translocase (Opie, 1979; Pepine & Welsch, 1995). As a result ATP is sequestered in the mitochondria, thereby activating negative feedback mechanism(s), indicating that the adenylate translocase is rate limiting. In light of these findings, the results from the present study are even more

intriguing because it may suggest an important role of the adenylate translocase system in the alterations to disease in patients with heart failure due to ischemic heart disease.

The Effect of Exercise Training

There are only five studies in the literature that have assessed the effects of physical training on skeletal muscle metabolism using 31P-NMR spectroscopy. The results of those studies all suggest an improvement in oxidative capacity reflected by a decrease in Pi/PCr, PCr/Pi or PCr/PCr+Pi at the same relative exercise intensity after training. The magnitude of change appears to be dependent on the choice of the in-magnet protocol, method of exercise training, and type of muscle group studied. Kent-Braun et al. (1990) exercised 7 healthy volunteers for a period of 8 weeks. Training consisted of wrist curl exercise performed 5 days per week. An in-magnet protocol to evaluate skeletal muscle metabolic adaptations to training consisted of a performance test of 10 min, followed by a ramp test. The results indicate a significant increase in work-output on the 10 min. performance test, and an increase in the work-energy cost relationship on the ramp test, as reflected by a 30% reduction in the Pi/PCr ratio following training. These data suggest that the training program resulted in an increased potential for oxidative metabolism. Minotti et al. (1990) trained five healthy volunteers for approximately 41 days using a similar exercise protocol as Kent-Braun et al. (1990). The objective of this study was to determine the effect of localized training on forearm Pi/PCr, pH, and blood flow at submaximal workloads. The results indicated that forearm training resulted in a lower Pi/PCr at identical submaximal workloads, and that this

improvement was independent of changes in muscle mass, blood flow, and VO_{2peak}. In a subsequent study Minotti et al. (1990) trained five men with heart failure for a period of 28 days. Subjects performed unilateral (non-dominant arm) wrist flexion exercise 6 days per week. As in the study with the healthy volunteers skeletal muscle metabolic responses were studied at submaximal workloads. The training regimen did not affect systemic hemodynamics or raise norepinephrine or lactate levels. Measurements of systemic exercise capacity and of forearm muscle cross-sectional area, and blood flow did not change following training. Yet, wrist flexor endurance increased 2- to 3-fold, and was associated with a slower rise in Pi/PCr. These findings demonstrate that skeletal muscle energetics can be improved without altering cardiac performance. Stratton et al. (1994) further confirmed these findings in 7 heart failure patients showing a reduction in skeletal muscle acidosis and PCr utilization during exercise following a one month wrist flexor training protocol. The only study which has examined the effects of exercise training in heart failure in skeletal muscle other than the forearm wrist flexors is a study by Adamopoulos et al. (1992). In this study 12 patients underwent 8 weeks of home-based exercise training on a stationary cycle. Training produced an increase in incremental plantar flexion exercise tolerance. After training, PCr depletion and the increase in ADP during exercise were significantly reduced. Furthermore, the authors reported a 25% increase in the PCr/PCr+Pi ratio indicating a substantial correction of the impaired oxidative capacity of skeletal muscle following the training period.

The present study confirms and further extends previous work in this area. Following a 16 week exercise training protocol, which included walking activities

performed 3 days per week, there was a significant improvement in skeletal muscle metabolic responses to identical submaximal workloads. This data demonstrates that exercise training serves as a significant stimulus to reverse the skeletal muscle metabolic alterations in patients with heart failure.

Evidence of Skeletal Muscle Metabolic Adaptations during Exercise

This study is the first to report a significant reduction of 19% in the Pi/PCr ratio during a low intensity workload (25% MVC) following a period of exercise training in patients with heart failure. It is thought that the 19% reduction in Pi/PCr ratio reflects an increased capacity of the exercising muscle to produce ATP from oxidative metabolic pathways. In contrast, the Pi/PCr ratio at peak exercise for the high intensity workload was not significantly altered following training. It is difficult to compare the magnitude of change in this study to previous findings because of different training regimens, in-magnet protocols, exercise intensities, muscle groups, and patient population. Minotti et al. (1990) reported a 55%, 50% and 25% reduction in Pi/PCrex, at workloads of 5, 23, and 48 J.min-1, respectively, following a 6 week wrist flexor exercise training program in healthy volunteers. Kent-Braun et al. (1990) reported a 30% decrease in Pi/PCr at the end of a 10 minute performance test following training. Neither study define the intensity of the work load used in the magnet, thereby complicating the interpretation of the data.

Comparison of the findings of this study to the three studies which have described the metabolic changes to exercise training in heart failure patients is also somewhat complicated. Minotti et al. (1990) reported a 25% reduction in Pi/PCr_{ex} during submaximal work loads following the 1 month wrist flexor exercise training regime.

Stratton et al. (1994) and Adamopoulos et al. (1992) used a slightly different ratio (i.e. PCr/PCr+Pi) to describe oxidative metabolism and noted a 15% and 20% improvement during a 75% of MVC and incremental work bout, respectively.

Thus, the findings from the present study appear to follow the same pattern observed by Minotti et al. (1990), Stratton et al. (1994) and Adamopoulos et al. (1992) indicating that a substantial correction of the oxidative capacity of skeletal muscle in patients with heart failure can be achieved through exercise training.

The intramuscular pH during the low and high intensity work bout was not affected by exercise training in this study. This is probably not too surprising since pH did not change dramatically during low intensity exercise, whereas the endpoint for the high intensity workload was based on volitional fatigue. Yet, Kent-Braun et al. (1990) did report a statistically significant increase in intramuscular pH following training using a ramp test in healthy adults. Stratton et al. (1994) also observed higher intramuscular pH values (not statistically significant) for all subjects at all incremental exercise stages. It is postulated that the higher pH after training reflects enhanced aerobic metabolism, as evidenced by a decreased need for glycolysis. On the other hand, no changes in intramuscular pH were observed in healthy volunteers (Minotti et al., 1990) and heart failure patients (Minotti et al., 1990) during submaximal workloads following training. Adamopoulos et al. (1992) also reported no significant changes in the pH response following training. The reason for the discrepancy is not clear but may be related to different patient populations, sample sizes, in-magnet protocols, muscle groups, training regimens, and technical considerations. It is important to note that the majority of

previous ^{31}P NMR spectroscopy studies have employed forearm exercise protocols. Generally, these studies have noted lower exercise values for pH compared to leg exercise protocols. Study protocols which induce a lower pH response may subsequently have a greater potential for improvement after training.

Although the intramuscular $H_2PO_4^-$ during the low intensity work bout was not statistically different from pre to post training, the percent increase appeared to be consistently lower in the trained group. It is possible that a larger sample size would result in a statistical significant difference. On the other hand, a statistically significant difference of 30% in intramuscular $H_2PO_4^-$ accumulation was observed following training during the high intensity workload. It is postulated that the reduction in $H_2PO_4^-$ production could have contributed to the increase in the in-magnet exercise time following the training period. There are currently no other studies which have determined the effect of exercise training on $H_2PO_4^-$ in healthy or heart failure subjects. Because of the possible important implications of $H_2PO_4^-$ in the contractile process, further studies are certainly warranted.

Evidence of Skeletal Muscle Metabolic Adaptations following Exercise

As previously mentioned, data from the present study demonstrate that PCr_{res} is significantly prolonged following both low and high intensity exercise in patients with heart failure. PCr_{res} (T1/2) were similar between the TR and NTR subjects prior the 16 week intervention. However, exercise training resulted in a 26% and 30% improvement in PCr_{res} (T1/2) following the low and high intensity workloads. In contrast, no changes in PCr_{res} (T1/2) were noted in NTR.

Only one other study has reported an enhanced rate of PCr_{res} (T1/2) following exercise training in heart failure (Adamopoulos et al., 1992). In this study, the PCr_{res} (T1/2) increased approximately 35% from 53.0 to 34.0 sec. In the present study, the pretraining average PCr_{res} (T1/2) following the low and high intensity exercise condition was approximately 66.0 sec and increased to 47.0 sec after training. Although, the reason for a slightly higher PCr_{res} (T1/2) prior to training is difficult to explain, disease severity and duration may have contributed to the observed differences between studies. On the other hand, it is encouraging to note that the PCr_{res} (T1/2) were similar following both the low and high intensity workloads, as this confirms the notion that PCr_{res} is independent of the intensity of the exercise (Meyer, 1988).

The enhanced PCr_{res} following training can not be explained by a change in muscle acidosis, or ATP depletion. In the present study the decrease in muscle pH during the submaximal workloads were not statistically different between the TR and NTR groups at any point during the study. Furthermore, no statistically significant changes in ATP were noted during the low and high workloads or following training. This suggests that the difference in PCr_{res} is a function of a different rate of net rephosphorylation of ADP following a period of exercise training in patients with heart failure.

The decrease in half-times in ATP/ADP*Pi in the exercise group may provide yet another index of metabolic change in skeletal muscle following exercise training. The present study is the first to suggest that ATP/ADP*Pi recovery kinetics are altered following training. Mean half-times for ATP/ADP*Pi following exercise decreased 30% and 37% respectively following low and high intensity exercise in the patients in the

trained group. As previously discussed, the observed decrease in ATP/ADP*Pi half-time recovery kinetics is thought to reflect (1) an increased movement of ATP hydrolysis products into the mitochondrial matrix, (2) an increase in mitochondrial volume or density, and/or (3) an increase in mitochondrial enzyme activity and/or concentration.

Although, the precise mechanism for improvement of oxidative metabolism is not clearly understood, the reduced Pi/PCr_{ex}, the increase in PCr_{rec}, and increased rate of ATP resynthesis from ADP and Pi following exercise probably reflects an increase in number of mitochondria, enzyme activity, improved ability to shuttle the hydrolysis products across the mitochondrial membrane, or a combination thereof.

Perception of Quality of Life

One of the most important findings of this study is the improved perception of quality of life. Data from this study indicated that the weighted scores for energy, physical mobility, and emotional reactions were markedly higher in the heart failure patients compared to those reported for healthy individuals in other studies. For example, the mean scores for energy, physical mobility, and emotional reactions in a group of healthy individuals over 65 years old were 5.07, 5.66, and 1.40, respectively (Hunt et al., 1981). In the present study the mean scores for energy, physical mobility, and emotional reactions prior to exercise training were 40.42, 22.62, and 26.49, respectively. The values reported for this patient population appear to fit the data from O'Brien et al. (1988). O'Brien et al. (1988) studied 48 heart failure patients awaiting cardiac transplantation. Patients in that study had a weighted score of 76.0 for energy, 51.2 for physical mobility,

and 39.2 for emotional reactions. The difference between studies is probably due to the fact that all the patients in O'Brien's study were in end-stage heart failure.

After 16 weeks, a consistent reduction in the weighted scores for energy, physical mobility, and emotional reactions was noted in the heart failure patients randomized to the training group. This study is the first to use the Nottingham Health Profile to monitor changes in quality of life in patients with heart failure following exercise training. In the study by O'Brien et al. (1988) an 80%, 74%, and 83% reduction in the mean scores for energy, physical mobility, and emotional reactions was noted in heart failure patients 3 months following cardiac transplantation. The percent reduction in the mean scores for energy, physical mobility, and emotional reactions in the heart failure patients following exercise training in this study were quite comparable at 74%, 44%, and 55%, respectively. One other study has reported improvements in quality of life (there was no mention of the survey used) following exercise training in heart failure (Kavanaugh et al., 1992). In this study, the improved perception in quality of life was closely related to the change in VO_{2peak}. In summary, it appears that an exercise training program improves the perception of quality of life in patients with heart failure.

Clinical Implication

Optimal management of patients with heart failure requires an understanding of the role of the many compensatory adaptations to the disease in contributing to exercise intolerance and chronic fatigue. The clinical contribution of the present study is to provide further insight in the clinical severity of heart failure. In addition, this study offers additional information regarding the ability of heart failure patients to adapt to a

period of exercise training. In combination these findings may help improve the therapeutic approach to this very important clinical problem.

The assessment of cardiac function during upright exercise has significant clinical implications. Walking continues to be the dominant activity for the majority of heart failure patients. Yet, very few studies have reported on the cardiac responses during walking activities. Traditionally, the assessment of cardiac function is assessed during a supine or semi-recumbent position. The information obtained in this study indicated a marked drop in cardiac output from a supine to upright position, followed by a blunted increase with exercise. This finding may explain some of the symptoms of dizziness experienced by heart failure patients when going from a supine or sitting position to standing. Further studies should determine if the changes in cardiac function during transition from one position to another is related to a loss in baroreceptor sensitivity.

The finding that the pre-exercise neurohumoral angiotensin II, arginine vasopressin, aldosterone, and atrial natriuretic peptide were all elevated suggests that current pharmacotherapy may not be adequate in these patients. Recognizing that neurohumoral hyperactivity carries an ominous prognosis suggests that the renin-angiotensin-aldosterone systems requires more aggressive pharmacotherapy. The results of such aggressive therapy with ACE-inhibitor has clearly shown to significantly reduce mortality and increase functional capacity in patients with heart failure. The reduction in pre-exercise angiotensin II, arginine vasopressin, aldosterone, and atrial natriuretic peptide following exercise training indicated a remarkable similarity between

ACE-inhibition and physical training. In light of that fact the clinical importance of exercise training could be improved prognosis.

The data from the present study clearly indicated that abnormal skeletal muscle energetics contributed to the exercise intolerance observed in these patients. However, evidence from this study also offer further insight into the etiology of the symptoms of chronic fatigue experienced by so many patients with heart failure. Many essential activities of daily living require relative short bouts of muscular activity. The finding that patients with heart failure have markedly elevated $H_2PO_4^-$ and prolonged recovery during and following short bouts of exercise may play a significant role in the development of symptoms of fatigue. Additional studies are warranted to further confirm these findings and determine the relationship to functional ability in patients with heart failure. The enhanced metabolic recovery kinetics following training may have important implications in improving the ability of heart failure to perform activities of daily living. One of the cardinal symptoms in heart failure is chronic fatigue. The fact that exercise training resulted in significant improvements in the metabolic profile during and following a short-term work bout and a significant increase in overall exercise tolerance indicates the important role of such a treatment strategy.

In light of the fact that exercise capacity is a powerful predictor of survival in heart failure the clinical implication of exercise training should be self-evident. By virtue of increasing VO_{2peak}, exercise training may improve prognosis in heart failure. Clearly, this study does not provide conclusive data on the effects of exercise training on prognosis in heart failure. However, several lines of evidence suggest that exercise

training may improve prognostically important variables and that the time has come to develop and implement a mortality and morbidity outcome trial.

Consideration for Future Research

A major emphasis of the present study was to determine the manner in which the compensatory adaptations to heart failure change during an acute exercise bout and whether exercise training can be a beneficial treatment strategy for patients with heart failure. The importance of this study relates to the fact that it is the compensatory adaptations that eventually sow the seed for a series of maladaptive processes which lead to a decompensated state or even end-stage heart failure (Zelis, 1991). Yet, these same compensatory adaptations are initially protective and prevent blood pressure from falling when the failing heart cannot adequately increase cardiac output. It is this apparent paradox which seriously complicates the treatment and management of the heart failure patient. For example, one could ask the question whether it is in the best interest to the patient to reverse the peripheral compensatory adaptations and allow skeletal muscle to increase the demand on a "failing" heart (Minotti & Massie, 1992). It would certainly seem that if reversal of the compensatory adaptations would occur too rapidly, this could result in devastating consequences. Thus, future studies should attempt to further determine to what degree the compensatory adaptations in heart failure are inherent to the disease or to other contributing factors such as physical deconditioning and/or malnutrition. As a result of such studies treatment strategies could develop to protect the compensatory adaptations aimed at optimizing cardiocirculatory performance, yet delay

the maladaptive processes which lead to a decompensated state or even end-stage heart failure.

The manner in which skeletal muscle adapts as a result of chronic heart failure is an important area for future studies. Sullivan et al. (1989) noted that despite the finding that skeletal muscle blood flow during exercise was reduced in both patients with chronic heart failure and peripheral vascular disease, the stimulus inducing skeletal muscle adaptations appeared to be very different in the two disorders. In fact, muscle biopsy data supports an increase in the markers of oxidative metabolism in peripheral vascular disease (Regensteiner et al., 1993), whereas heart failure patients exhibit global oxidative down regulation. This contrasting adaptation to a similar low blood flow environment suggests the involvement of different controllers and signals. It appears that local tissue controllers may contribute to the skeletal muscle adaptations in peripheral vascular disease. However, in heart failure it may be that the local signals are overwhelmed by other signals (cardiac, neural, or pharmaceutical) which results in a vastly different adaptation. An intriguing hypothesis which is under current investigation is that the skeletal muscle abnormalities in heart failure develop to prevent an individual from placing to great a demand on the cardiopulmonary system. This phenomena of metabolic shut-down may be similar to myocardial stunning and hibernation. The extent of this occurring in skeletal muscle is not known but certainly deserving of further investigation. An additional question which is currently being considered by this laboratory concerns the efficacy of exercise training following improvement of cardiac function secondary to positive inotropic agents, in patients with heart failure. The use of positive inotropes to

enhance cardiac contractility in heart failure continues to stimulate great discussion and debate. Yet, despite the many questions about the efficacy and safety of these agents, the use of "Dobutamine-Holidays" to increase cardiac function in heart failure patients is not uncommon. In fact, patients receiving such treatment often feel much improved for a period of 10 to 12 weeks, after which their clinical symptoms often return. It appears that the period immediately following the treatment could provide an excellent window of opportunity to assess the changes in the compensatory adaptations to the disease and whether exercise training could prolong the observed benefits and reduce the rate of re-hospitalization. Such research could also help justify the use of a structured cardiac rehabilitation program with reimbursement for the heart failure patient. Currently no such programs or reimbursement are available for patients with a diagnosis of heart failure.

There are several other important clinical questions that remain unanswered at this time. For example, should exercise training be attempted in all patients with heart failure. To date, the majority of studies involving exercise training and heart failure patients have not specifically addressed the issue of the etiology of disease. In addition, are the exercise responses similar in patients with different etiologies of heart failure. Future studies are certainly necessary to determine if exercise training is beneficial for all patients with heart failure, secondary to idiopathic etiologies, hypertensive heart disease, and valvular disorders.

Are there other exercise modalities that could be beneficial to the heart failure patient? To date, all studies have utilized dynamic "aerobic" type of activities. There is

no information available regarding the potential benefit of resistive exercises in heart failure. Such exercises may be extremely important in improving muscle strength, thereby allowing the patient to perform the activities of daily living with greater ease. Further studies are necessary to determine the safety and efficacy of such exercises in the heart failure patient.

Other studies are in progress which are determining the efficacy of exercise training in patients who developed heart failure secondary to myocardial infarction. The timing of exercise may be important in determining the effect of exercise training on ventricular remodeling, hibernating and/or stunned myocardium. Finally, further research is warranted to determine the effect of standard and new pharmacotherapy on the compensatory adaptations to heart failure during physical activity. Exercise training in combination with pharmacotherapy may in fact produce significant improvements in the functional abilities of the patients, and reducing the morbidity and mortality associated with the disease.

Understanding the key controllers and signal systems which contribute to the heart failure syndrome will ultimately result in the development of improved treatment strategies for this disease. It appears the time has come to initiate a multi-center clinical trial to determine the effects of a long-term exercise training program on morbidity and mortality in heart failure.

Summary and Conclusions

Heart failure is at present the nation's most rapidly growing cardiovascular disorder, and is a major cause of morbidity and mortality. Heart failure is a syndrome in

which a reduction in function results in a series of time-dependent compensatory adaptations. Although, these compensatory changes are often remarkably effective in normalizing cardiocirculatory function, they exact a price which results in a marked inability of patients to carry out activities of daily living, care for themselves, and support their families. The present research examined the physiologic responses to an acute bout of exercise and to determine whether a 16 week exercise training program could represent a beneficial treatment strategy for patients with heart failure.

This study demonstrated that the physiologic responses to an acute bout of exercise in a patient with heart failure were characterized by a reduction of the hemodynamic and neurohumoral reserve capacity. The stroke volume response during different intensities of exercise was blunted in the patients with heart failure compared to those reported for healthy individuals. This resulted in a greater reliance on the heart rate response to increase cardiac output with exercise. The peak exercise responses in the patients with heart failure were further characterized by a reduction in HR_{peak}, systolic blood pressure, rate pressure product and O_2pulse compared to age-matched controls. Furthermore, pre-exercise venous blood concentration for angiotensin II, atrial natriuretic peptide, arginine vasopressin, and aldosterone were all elevated compared to healthy individuals. This study also demonstrated that patients with heart failure have impaired skeletal muscle energetics during exercise, and a prolonged metabolic recovery following exercise. It is thought that the reduced hemodynamic and neurohumoral reserve capacity and the impaired skeletal muscle metabolic responses during and following exercise contribute significantly to the marked exercise intolerance and chronic fatigue observed

in patients with heart failure. Although, the data from the present study confirms previously reported work, there are also several unique findings which may contribute to a better understanding of the heart failure syndrome. In addition, this study is the first randomized trial of this magnitude to report the beneficial role of exercise training on exercise capacity, tolerance and perception of quality of life in patients with heart failure. Although there are many factors which could have contributed to the observed changes in exercise tolerance and capacity in this patient population, this study provides strong evidence that exercise training results in a widening of the hemodynamic and neurohumoral reserve capacity. It is thought that the gradual reversal of the time-dependent compensatory changes to heart failure contributed significantly to the increase in exercise tolerance and VO_{2peak}.

Exercise Capacity and Tolerance

The present study confirms previous data demonstrating a significant reduction in exercise capacity and tolerance in patients with heart failure. Following a 16-week exercise training program a significant 31% increase in exercise tolerance, as defined by exercise time, and 23% increase in exercise capacity, defined by VO_{2peak}, was noted in those patients randomized to the exercise training program compared to pretraining values and the non trained heart failure group. This study is the first randomized trial of this length to report the beneficial role of exercise training on exercise capacity and tolerance.

Cardiac Function

The cardiac output, and stroke volume response to an acute bout of exercise, in this study, is blunted in patients with heart failure. This suggests that patients with heart failure have a narrow cardiac output reserve capacity which is certain to play a significant role in the exercise intolerance observed in these patients. Although, a narrow cardiac output reserve capacity with exercise has been previously reported, this study is the first to determine cardiac function during submaximal upright exercise in patients with heart failure. In addition, the chronotropic reserve for patients with heart failure was significantly less compared to age-matched controls during a SL-GXT. It is thought that the reduced chronotropic reserve has a significant impact on exercise performance since the increase in cardiac output in heart failure patients at higher intensities of exercise appears to be largely dependent on an increase in heart rate as stroke volume was shown to decline.

A disappointment of the present study was the inability to adequately evaluate cardiac function following exercise training. The use of Doppler echocardiography during upright exercise was significantly affected by technical difficulties and the small number of patients in whom adequate cardiac images and blood flow assessments were collected. However, exercise training did result in a slight increase in the chronotropic reserve in patients with heart failure. Clinically, this could translate in the patient performing more activities of daily living at a lower percent of the reserve capacity which could reduce the amount of fatigue associated with physical exertion.

Circulatory Function

In the present study plasma angiotensin II, arginine vasopressin, aldosterone, and atrial natriuretic peptide were all elevated compared to a healthy control group previously studied in this laboratory using similar standardization techniques and assay procedures. This indicates that standard pharmacotherapy, including ACE-inhibitors, diuretics and digitalis, may not be adequate in normalizing neurohumoral levels in this group of heart failure patients. The fact that excessive neurohumoral activation is a major determining factor in the evolution from compensated ventricular dysfunction to end-stage heart failure underscores the importance of more appropriate and aggressive pharmacotherapy to modulate neurohumoral activity.

A unique finding of this study is the apparent reduction in pre-exercise neurohumoral concentrations following 16 weeks of exercise training. A consistent reduction in angiotensin II, aldosterone, arginine vasopressin, and atrial natriuretic peptide was observed in those patients randomized to the exercise training group. This study is the first to report such a change. Although, the mechanism for the reduction in the pre-exercise fluid-regulatory hormones following training is not clear, it may indicate a potential protective role of exercise training in patients with heart failure.

Skeletal Muscle Function

Some of the symptoms of chronic fatigue in heart failure have been attributed to impaired oxidative metabolism in skeletal muscle. The present study confirms work by others and offers new insight regarding the metabolic abnormalities in skeletal muscle in patients with heart failure. In the present study impaired oxidative metabolism, defined

by a rapid and greater rise of the Pi/PCr ratio, was noted during low intensity exercise. The greater rise in Pi/PCr with exercise indicates a greater reliance on glycolytic pathways to meet energy demands. The increased reliance on these pathways is thought to result in an increase in Pi and H^+ production, two potential factors involved in the early onset of skeletal muscle fatigue. Furthermore, this study demonstrates that exercise results in a significantly greater increase in $H_2PO_4^-$ in heart failure patients compared to age-matched controls. This significant increase was associated with a greater perceived exertion during low intensity exercise, and early fatigue during the high intensity work bout. The marked elevation in intramuscular $H_2PO_4^-$ with exercise is proposed to contribute to the marked exercise intolerance and symptoms of muscular fatigue exhibited during short duration activities in patients with heart failure, secondary to interference with the force-producing step of the cross-bridges by shifting the distribution of cross bridges towards those states with a full complement of bound products (ADP and Pi). Such a shift would lead to a decrease in the available number of force-producing cross bridges, a reduction in developed tension, and muscular fatigue.

Data from the present study also indicates abnormal skeletal muscle metabolic recovery in patients with heart failure. The PCr_{res} was significantly prolonged following both low and high intensity exercise in patients with heart failure compared to controls. This finding also confirms previous research by other investigators. However, another unique finding of this study is the evidence of prolonged recovery of the ATP hydrolysis products (ADP and Pi). These findings not only confirm that skeletal muscle energetics is altered during exercise but also indicates abnormal recovery kinetics. Thus, these

findings do not just provide insight about the marked reduction in exercise capacity, but they also offer important information regarding the symptoms of chronic fatigue in patients with heart failure.

This study is the first to report a significant reduction of 19% in the Pi/PCr ratio during a low intensity workload (25% MVC) following 16 weeks of exercise training in patients with heart failure. It is thought that the 19% reduction in Pi/PCr ratio reflects an increased capacity of the exercising muscle to produce ATP from oxidative metabolic pathways. Furthermore, a significant reduction in intramuscular $H_2PO_4^-$ accumulation was observed following training during the high intensity workload. It is postulated that the reduction in $H_2PO_4^-$ production could have contributed to the increase in the in-magnet exercise time following the training period. Exercise training also resulted in an improvement in skeletal muscle recovery kinetics as evidenced by a significant decrease in the PCr_{res} (T1/2) and half-times for ATP/ADP*Pi following low and high intensity workloads. Although, the precise mechanism for improvement of oxidative metabolism is not clearly understood, the reduced Pi/PCr_{ex}, the increase in PCr_{rec}, and increased rate of ATP resynthesis from ADP and Pi following exercise probably reflects an increase in number of mitochondria, enzyme activity, improved ability to shuttle the hydrolysis products across the mitochondrial membrane, or a combination thereof.

Perception of Quality of Life

Perhaps one of the most intriguing and significant findings of this study was a consistent reduction in the weighted scores for energy, physical mobility, and emotional

reactions after 16 weeks of exercise training in the heart failure patients randomized to the training group.

Conclusion

In conclusion, the heart failure syndrome is characterized by a myriad of compensatory adaptations which contribute to the clinical severity of the disease. Exercise training presents a profound stimulus in reversing several of these compensatory adaptations resulting in a significant increase in exercise tolerance and capacity, as well as perception of quality of life in patients with heart failure. It appears the time has come to initiate a multi-center clinical trial to determine the effects of a long-term exercise training program on morbidity and mortality in heart failure.

APPENDIX

INFORMED CONSENT TO PARTICIPATE IN RESEARCH

J. HILLIS MILLER HEALTH CENTER
UNIVERSITY OF FLORIDA
GAINESVILLE, FLORIDA

You are being asked to participate in a research study. This form is designed to provide you with information about this study and to answer any of your questions.

1. TITLE OF RESEARCH STUDY

"The Effect of L-Carnitine Supplementation on Patients With Chronic Heart Failure Before and After Exercise Training"

2. PROJECT DIRECTOR

Carl J. Pepine, M.D. (904) 846-0602

3. THE PURPOSE OF THE RESEARCH

The purpose of this study is to evaluate the effect of L-carnitine on cardiac and skeletal muscle function at rest, during exercise and following exercise training in a group of patients with congestive heart failure. In addition, the effect of L-carnitine and exercise training on measures of quality of life will be assessed in this group of patients.

4. PROCEDURES FOR THIS RESEARCH

If you agree to participate in this study you will be seen in clinic initially for a medical history, physical examination, and quality of life assessment.

If you meet all the entry criteria you will be asked whether you are willing to participate in the exercise component of the study. If you indicate you are willing to participate in the exercise portion of the study you may or may not be assigned to an exercise group. If you indicate you are not able to commit to the exercise component of the study (due to transportation, time or finances), you are still eligible to participate in the non-exercise component of the study.

You will then be asked to perform an exercise test on a treadmill to determine your ability to exercise. While walking on the treadmill you will be asked to exhale in a special tube so that oxygen and carbon dioxide levels can be measured. During the test you will be connected to a heart monitor and your blood pressure will be taken every two minutes. In addition a small sample of blood will be drawn from a vein in your arm before and after exercise for laboratory studies. You will perform this test at the Center for Exercise Science, located on the campus of the University of Florida, under the supervision of a physician.

Following these test you will be randomly assigned (much like the toss of a coin) to receive either the study medication or a placebo (an inactive substance). The medication will be taken three times a day. Neither you or your doctor will know which you are taking. If it becomes necessary to know which you are taking a coded list will be kept in the pharmacy. You will take the medication for the duration of the study which is to last six months.

After one month you will be asked to return to the Center for Exercise Science located on campus for further testing. There you will have a brief physical examination, and a quality of life assessment. Then your body composition will be assessed using skinfold fat calipers. During this test a staff member will determine how much fat is on your body by pinching and measuring the thickness of your skin with the aid of a measuring device called a caliper. Seven measurements will be taken at standard locations on your body. You will also perform a second exercise treadmill test to see how much oxygen your body uses during exercise.

After three days you will be asked to report to the VAMC, Non-invasive Cardiology Laboratory to have your heart function evaluated by what is known as echocardiography. This is a non-invasive technique that uses ultrasound to form a picture of the heart. During this evaluation you will also be asked to exercise on a treadmill. The exercise portion of this test involves having you walk on a treadmill at three different levels of work. Each level of work will be slightly different from each other and will range from moderate to hard work. Before the start of exercise and after each level of work a physician will place a small ultrasound probe on your chest and take a picture of your heart. Throughout this test you will be connected to an EKG monitor and have your blood pressure taken.

In two days you will be asked to return to the VAMC, MRI Laboratory to have a test that involves evaluation of how efficiently your muscles work. This will involve pushing your foot against a pedal while lying in a special imaging device called a Nuclear Magnetic Resonance Magnet.

Following two more days you will again return to the Center for Exercise Science where you will be asked to perform a walking test at the same levels of work as during the ultrasound test. You will be asked to walk for three minutes at each work load (or until you start noticing discomfort). Between each work load you will be allowed to rest for five minutes. While walking on the treadmill you will, again, be asked to exhale in a special tube so that oxygen and carbon dioxide levels can be measured. In addition during the last minute of each exercise bout you will be asked to breathe from a bag that contains

a gas mixture. The gas mixture consists of 0.5% acetylene, 45% oxygen, and 10% helium in nitrogen. You will breathe from the bag for approximately eight seconds after which you will again breathe normal room air. This procedure allows us to measure approximately how much blood the heart pumps. During the test you will be connected to a heart monitor and your blood pressure will be taken every two minutes. In addition a small sample of blood will be drawn from a vein in your arm before and after exercise for laboratory studies.

If you indicated at the beginning of the study you could not commit to the exercise component of the study (due to transportation, time or finances), you will be asked to continue to take the study medication for 4 more months. Following the 4 months you will again be evaluated using the same testing procedures described above.

If you agreed to participate in the exercise program you will be randomized to an exercise or non-exercise group at the end of the first month of the study. The exercise training program will last 16 weeks and you will continue to take your medication daily. Half of the patients will exercise in the training program and the other half will be asked not to make any changes in their physical activity and exercise until the completion of the research study. The investigator will tell you which group you are in.

If you are in the group who are to have exercise training, the training sessions will be carried out three times per week for a total of 16 weeks. Each training session will consist of either walking on the treadmill or stepping on a stair climber. You will be given instructions concerning warm-up and cool-down techniques, as well as how to monitor the intensity of exercise by feeling your pulse and use of a rating of perceived exertion scale. All exercise will be supervised by staff at the Center for Exercise Science.

Regardless of your group assignment you will be seen in clinic every month to assess your current status.

At the end of 16 weeks your cardiac function will again be evaluated using echocardiography and your leg muscle function with the Nuclear Magnetic Resonance Magnet. In addition a complete physical examination, a quality of life assessment, a treadmill exercise test will be performed and blood drawn for laboratory studies. At this time your participation in the study will be complete.

5. POTENTIAL RISKS AND DISCOMFORTS

If you wish to discuss these or any other discomforts you may experience, you may call the Project Director listed in #2 of this form.

Study drug: L-carnitine is a naturally occurring substance which is essential in the metabolism of fat. Because L-carnitine is a substance that is normally produced by the body, taking the drug is expected to cause few side effects. Side effects that have been reported in patients with various heart disorders consisted primarily of temporary nausea and vomiting, abdominal cramps, and diarrhea. These effects are usually resolved with a reduction in the carnitine dosage.

Exercise Training: Cardiac complications during exercise training for patients with cardiac disease include cardiac arrest, irregular heart beats, heart attack, blood clot to the lung, heart failure, chest pain, and fainting. One study that looked at 51,303 patients who exercised a total of over 2 million hours during the period 1980-1984 showed twenty one cardiac arrests (18 successfully resuscitated and 3 fatal) and 8 non-fatal heart attacks. The rate of complications were one cardiac arrest per 111,996 hours, one heart attack per 293,900 hours and one fatality per 783,976 hours of prescribed supervised exercise. The risk in this study will be minimized as a result of proper patient evaluation, education, and treatment, careful exercise prescription, appropriate degrees of ECG monitoring and well trained personnel capable of monitoring exercise and handling emergencies.

Nuclear Magnetic Resonance Imaging Magnet: Although high magnetic fields or rapidly changing magnetic fields or strong radiowaves can be hazardous, this device operates at such low magnetic fields and radiowaves that it has no known risks or hazards. Since the imaging equipment uses a magnet, you must not have any metal objects on your body (pacemaker, intracranial clips, coins, glasses, jewelry, etc).

EKG (Electrocardiogram): No risks are involved.

Exercise Treadmill Test (ETT): There are potential risks (approximately 2-3 per 10,000) associated with the exercise stress testing to be done. These include episodes of temporary lightheadedness, fainting, chest discomfort, leg cramps, and very rarely, heart attack. The checkup before the test, attendance of qualified personnel during the test, and emergency treatment readily available are all part of the safeguards included in the procedure.

Echocardiography: There is no known risk associated with this procedure.

Blood Draws: The risks of drawing blood from a vein include discomfort at the site of injection; possible bruising and swelling around the injection site; rarely an infection; and uncommonly, faintness from the procedure. Blood drawn each time will vary from 4 teaspoon to 8 teaspoons. The total amount drawn during the study will be approximately 24 tsp.

Acetylene Rebreathing: The gas mixture used for the rebreathing study does not have an unpleasant odor or taste. The procedure is generally not uncomfortable in part due to the short exposure time (only 8 seconds) and a high concentration of oxygen (45%) in the bag. The most common complaint with the procedure is the weight of the rebreathing apparatus (bag and stopcock) on the mouthpiece. To avoid this problem the bag will only be attached during the last minute of each exercise bout. However, if you do not feel comfortable at any time during the procedure we will stop.

6. POTENTIAL BENEFITS TO YOU OR TO OTHERS

You understand the benefits, which you might reasonably expect from taking part in this study, are from being extensively evaluated and giving your doctor a better picture of your medical condition. There is no guarantee that your participation will directly benefit you. Other patients with a similar condition may benefit from information obtained in

this study. You realize that you will receive the study medication and tests required for the study at no charge to you.

7. ALTERNATIVE TREATMENTS OR PROCEDURES, IF APPLICABLE

You understand that participation in this research study is voluntary and you have the alternative to not participate in the study or to withdraw from the study at any time without prejudice to you. Alternative treatment would be to continue with standard medical therapy currently available as decided by your doctor.

Choosing not to participate in this study will in no way affect your care.

ADDITIONAL INFORMATION

You understand that the study drug is not packaged in a container resistant to being opened by children and that you should exercise caution to keep the study drug out of their reach. I have been made aware that the drugs provided for this study will not always be packaged in child-resistant containers and I will exercise caution accordingly.

I have been informed that because this study involves articles regulated by the FDA (Food and Drug Administration), the FDA may choose to inspect records identifying me as a subject in this investigation.

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BIOGRAPHICAL SKETCH

Michael Andrew Welsch was born in Castricum, The Netherlands on May 21, 1960. He graduated from Bonhoeffer College in June, 1979.

In May 1984, he completed a Bachelor of Science degree at North Texas State University with a major in Physical Education. In August 1986, he completed the Master of Science degree in exercise physiology at North Texas State University.

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In August 1990, he entered graduate school at the University of Florida to pursue the Doctor of Philosophy degree with a major in exercise and sports sciences and a minor in physiology. His degree program will be completed in 1996. Following graduation, he will pursue an academic career.

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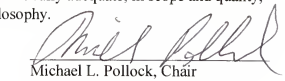

Michael L. Pollock, Chair
Professor of Exercise and Sports Sciences

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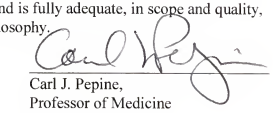

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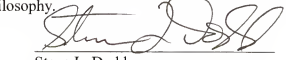

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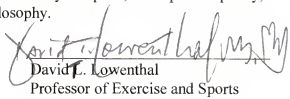

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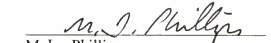

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This dissertation was submitted to the Graduate Faculty of the College of Health and Human Performance and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

December 1996

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